ENANTIOSPECIFIC TOTAL SYNTHESIS OF (-)-AGELASTATIN A AND EVALUATION OF ITS BIOLOGICAL PROPERTIES

by

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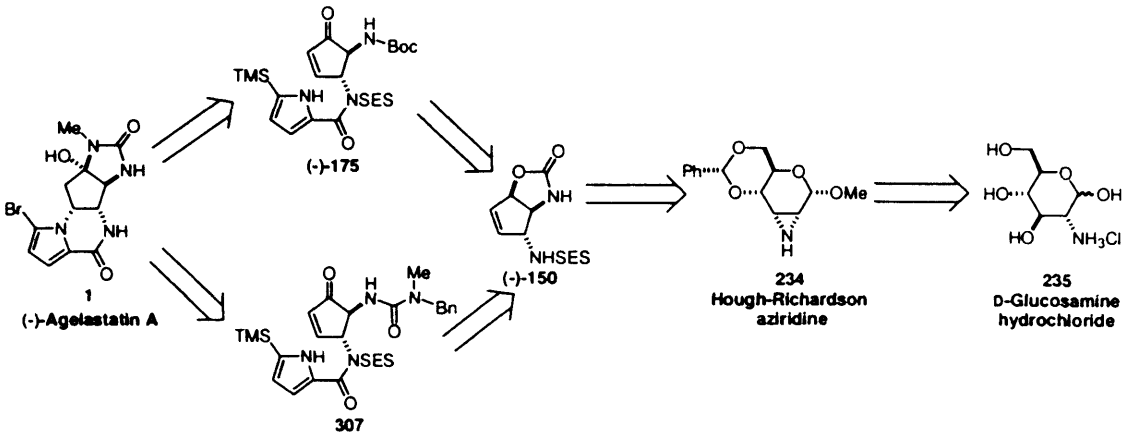
Abstract



(-)-Agelastatin A (**1**) is a tetracyclic alkaloid recently isolated from the marine sponge *Agelas dendromorpha*. It has powerful antitumour properties *in vitro* and *in vivo*, and is a selective inhibitor of the ubiquitous enzyme, glycogen synthase kinase 3β. It also exhibits insecticidal properties.

In this thesis, we describe an enantiospecific total synthesis of the cyclopentenone (-)-**175**, an advanced intermediate whose racemate had previously been converted into (±)-agelastatin A by Weinreb and co-workers. Our strategy exploited the chiral oxazolidinone **150** as a key intermediate, and commenced from the Hough-Richardson aziridine **234** (which is itself obtainable from D-glucosamine hydrochloride). Noteworthy reactions in the route to **150** include the regioselective *trans-diaxial* ring-opening of **234** with azide ion to set up the vicinal diamido functionality present in (-)-**175**, and the Grubbs-Hoveyda ring-closing metathesis reaction that is used to fashion its cyclopentene core.

We also describe a new synthetic endgame for converting (-)-**150** to (-)-agelastatin A *via* cyclopentenone **307**.

This new endgame has so far allowed 223 mg of (-)-agelastatin A to be prepared for detailed toxicological and biological evaluation. Some of the results of these studies are presented in this thesis.

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Abbreviations

Bn	Benzyl
Boc	*t*-Butoxycarbonyl
Bz	Benzoyl
CBz	Benzyloxycarbonyl
m-CPBA	*m*-Chloroperoxybenzoic acid
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DIAD	Diisopropyl azodicarboxylate
DIBAL	Diisobutylaluminium hydride
DIEA	*N,N*-Diisopropylethylamine (Hünig's base)
DMAP	4-Dimethylaminopyridine
DMDO	Dimethyldioxirane
DME	1,2-Dimethoxyethane
DMF	*N,N*-Dimethylformamide
DMSO	*N,N*-Dimethylsulfoxide
HMPT	Hexamethylphosphotriamide
HRMS	High resolution mass spectrometry
IBX	*o*-Iodoxybenzoic acid
IR	Infra-red
KHMDS	Potassium hexamethyldisilazide
LC_{50}	Median lethal dose 50
LiHMDS	Lithium hexamethyldisilazide
LRMS	Low resolution mass spectrometry
NaHMDS	Sodium hexamethyldisilazide
Ms	Methanesulfonyl
o-NB	*o*-Nitrobenzyl

NBS	*N*-Bromosuccinimide
NMO	*N*-Methylmorpholine *N*-oxide
PDC	Pyridinium dichromate
Ph	Phenyl
PPA	Polyphosphoric acid
Py	Pyridine
RT	Room temperature
SEM	[2-(Trimethylsilyl)ethoxy]methyl
SES	β-Trimethylsilylethanesulfonyl
TBAF	Tetra-*n*-butylammonium fluoride
TEA	Triethylamine
TES	Triethylsilyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TMS	Trimethylsilyl
Tol	Toluyl
TPAP	Tetra-*n*-propylammonium perruthenate
Ts	*p*-Toluenesulfonyl

Contents

Chapter 1: The Agelastatins and Related Marine Alkaloids

The utility of natural products as sources of novel structures for the discovery and the development of drug candidates is well established. A recent review by Newman and co-workers indicates that, in the area of cancer, over 60% of the drugs approved by the Food and Drug Administration over the period 1981-2002 could be traced back to a source of natural origin.[1] The diversity of the structures presented to us by Nature is well beyond the scope of the human mind, and this probably justifies the efforts made for the isolation and the structure elucidation of new compounds of natural origin.

1.1. Isolation of the Agelastatins

(-)-Agelastatin A (**1**, Figure 1) is an alkaloid of unprecedented structure, isolated by Pietra and co-workers from the marine sponge *Agelas dendromorpha* (order Axinellida, family Agelasidae), collected by dredging in the Coral Sea off New Caledonia.[2] Its absolute configuration, deduced by a combination of NMR and circular dichroism studies,[3] was assigned to be (5a*S*, 5b*S*, 8a*S*, 9a*R*). In the crude extract, agelastatin A cannot be separated from its dibrominated analogue, (-)-agelastatin B (*ca.* 20% in weight) (**2**, Figure 1). More recenltly, Molinski and co-workers reported the isolation of two additional congeners of the agelastatin family, (-)-agelastatin C and (-)-agelastatin D (**3** and **4**, Figure 1), from the West Australian sponge *Cymbastella sp.*[4] (-)-Agelastatin C features an additional 5b-hydroxyl group, whereas (-)-agelastatin D lacks the *N*-methyl group.

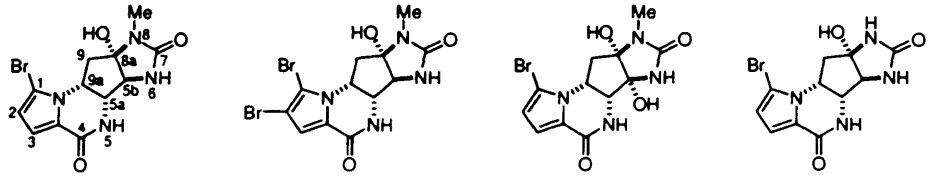


Figure 1. Structure of the agelastatin family members

1.2. Biological Properties of the Agelastatins

(-)-Agelastatin A has powerful cyotoxic effects against various tumour cell lines. Growth-inhibition tests for (-)-agelastatin A, and some of its semi-synthetic derivatives, were performed on an L1210 murine lymphocytic leukemia cell line and a subline that was resistant

to doxorubicin (L1210/Dx).[5] Similar assays were performed on a human KB nasopharyngeal cancer cell line. The results (Table 1) were expressed in terms of IC_{50} values (test compound dose causing 50% inhibition of cell growth in treated cultures relatively to untreated control).

Table 1. Cytotoxicity data (IC_{50}, µg/mL) against L1210, L1210/Dx, and KB tumour cells *in vitro* for (-)-agelastatin A and some of its derivatives

	L1210 IC_{50}	L1210/Dx IC_{50}	Resistance Index (ratio between IC_{50} values for L1210/Dx cells *vs.* L1210 cells)	KB IC_{50}
(-)-Agelastatin A	0.033	0.469	14.0	0.075
(-)-Agelastatin B	> 1	> 1	--	> 10
(-)-Debromo-agelastatin A	0.143	2.11	14.7	--
Doxorubicin	0.014	0.548	38.8	--

The data obtained so far have demonstrated that the monobrominated pyrrole ring system is optimal for cytotoxic activity. Cytotoxicity declines on alkylating or acylating any one of the N(5), N(6), or C(8a)-OH groups. Inversion of the C(5b)-C(8a) ring-junction stereochemistry also leads to a 3 to 4-fold decrease in antitumour activity, which suggest that there is a strict configurational requirement for the cytotoxicity.

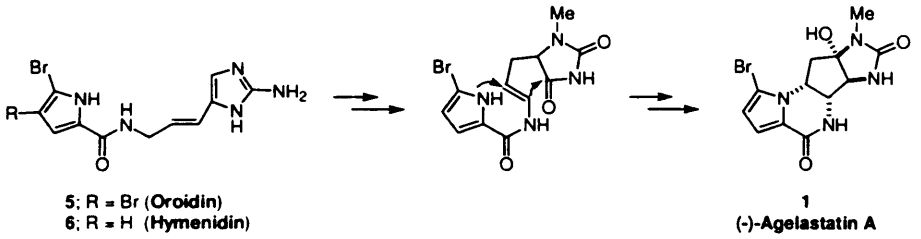
In vivo toxicity of (-)-agelastatin A was evaluated by intraperitoneal (*i.p.*) and intravenous (*i.v.*) administration of the natural product in mice inoculated with L1210 murine leukemia. The activity was evaluated in terms of percentage increase in median survival times in comparison with untreated controls. Increase of survival time was 63% at the dose of 2.6 mg/kg, after repeated *i.p.* administration; no activity was found after single or repeated *i.v.* administration.

The arthropod toxicity of (-)-agelastatin A was evaluated by Molinski *et al.*[4] They observed that it was highly toxic towards brine shrimp. Dose-response measurements against newly hatched brine shrimp gave an LC_{50} of 5.0 µM. (-)-Agelastatin A was also found to be insecticidal against the beet army worm, *Spodoptera exigua*, and the corn root worm, *Diabrotica undecimpunctata*. Larvae of both insects were fed on a diet treated with the alkaloid or solvent (control) and monitored for mortality over 4, 5, and 7 days. The 4-day and 7-day LC_{50}s of agelastatin A against beet army worm were 26 µg/mL and 20.3 µg/mL respectively, while for corn root worm, the 5-day and 7-day LC_{50}s were 37 µg/mL and 32 µg/mL. These values were comparable to a commercial preparation of the biopesticide *Bacillus thuringiensis* tested against beet army worms under the same conditions.

This toxicity is certainly related to the fish feeding deterrent activity of brominated pyrrole alkaloids present in Caribbean reef sponges of the genus *Agelas*.[6] More particularly, the sub-structure 4,5-dibromopyrrole-2-carboxylic acid was identified as a potently active compound against a common generalist fish, the bluehead wrasse *Thalassoma bifasciatum*, at the dose of 10 mg/ml. This confirms the ecological role of the pyrrole-imidazole alkaloids as defensive secondary metabolites of the marine sponges in which they are present.

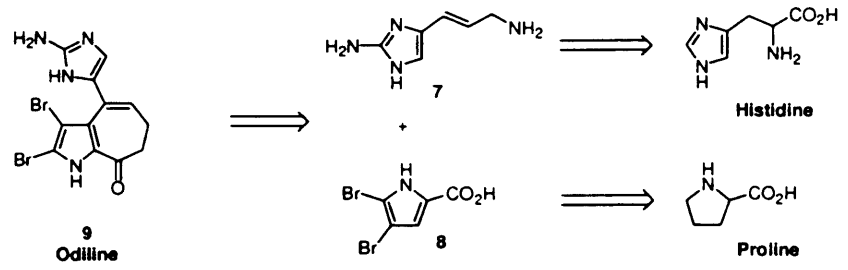
1.3. Biosynthetic Possibilities for Various Members of the Oroidin Family of Alkaloids

The unusual C_{11} highly fused pyrrole-imidazole framework present in (-)-agelastatin A (and its congeners) has led to suggestions that this compound is a member of the oroidin family of alkaloids, since oroidin (**5**, Scheme 1), isolated from *Agelas oroides*,[7,8] is historically the central member in a series of similar alkaloids. Pietra *et al.* suggested in their preliminary report that agelastatin A could be biogenetically derived from the oroidin analogue, hymenidin (**6**, Scheme 1).[2]



Scheme 1. A putative biosynthetic pathway for (-)-agelastatin from hymenidin

The first biosynthetic study of a marine sponge using a cell culture of *Teichaxinella morchella* (Axinellidae) was reported by Kerr *et al.*[9] They demonstrated by feeding studies using labelled proline and histidine that these amino acids are precursors of odiline (**9**) (syn: stevensine) via 3-amino-1-(2-aminoimidazolyl)-prop-1-ene (**7**) and 4,5-dibromo-2-carboxylic acid (**8**) (Scheme 2). This hypothesis is further supported by the recent isolation of clathramide A (**10**, Figure 2) from the sponge *Agelas clathrodes*.[10,11]



Scheme 2. The biogenetic precursors of odiline from the sponge *Teichaxinella morchella*

While the pyrrole part is generally accepted to originate from proline, alternative precursors for the aminoimidazole fragment have been proposed, such as homoarginine.[12,13,14] The latter hypothesis is reinforced by the recent isolation of *N*α-(4-bromopyrrolyl-2-carbonyl)-homoarginine (**11**, Figure 2) from the marine sponge *Agelas wiedenmayeri*.[13]

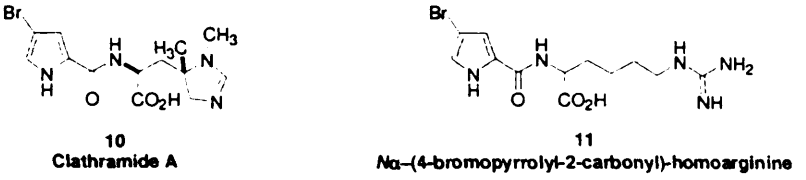
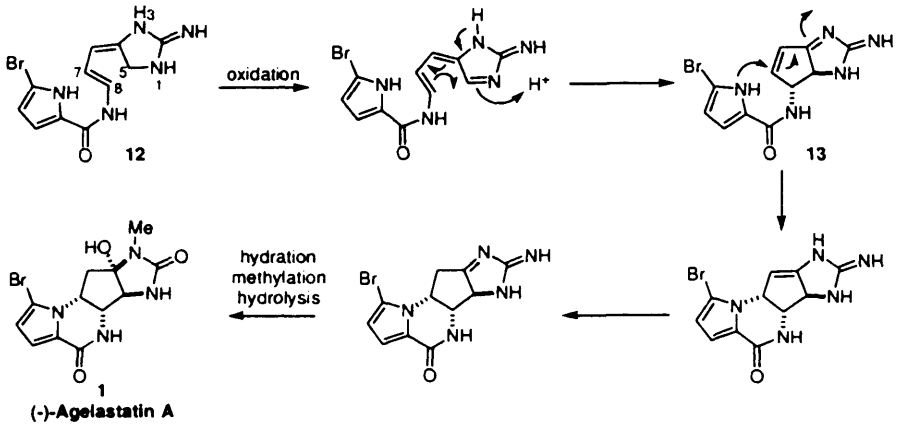


Figure 2. Putative intermediates for the biosynthesis of oroidin-like alkaloids

More recently, a universal chemical pathway to the oroidin-based pyrrole-imidazole alkaloids and their congeners was proposed by Al Mourabit and Potier.[15] They suggested that the members of the pyrrole-imidazole alkaloid family can be traced back to simple precursors such as **7** and **8**. These precursors can show ambivalent reactivity, which is responsible for the molecular diversity observed in this group of alkaloids. While on one hand, pyrrole-2-carboxylic acid and its 4- or 5-brominated derivatives such as **8** can exert their nucleophilicity at N(1) or C(3), on the other hand, tautomerism of the vinylogous aminoimidazole building block **7** can explain the ambident reactivity at several positions of this compound. Various tautomers form, and their behaviour is probably controlled by the enzymatic system responsible for the biosynthesis of these secondary metabolites, by virtue of it being able to exchange protons with its substrate.

The versatility of this system can then give rise to polycyclic metabolites through various combinations with pyrrolic building blocks and diverse modes of cyclisation. With regards to agelastatin A, Al Mourabit and Potier suggested that oxidation of the hymenidin tautomer **12** was the key step in the intramolecular cyclisation pattern (Scheme 3). After the first C(8)-C(5) cyclisation (biogenetic numbering) to give **13**, an unusual N(1)-C(7) connection can possibly occur; further transformation can then furnish agelastatin A (**1**) and its derivatives.



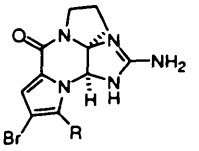
Scheme 3. Al Mourabit and Potier's biosynthetic pathway for (-)-agelastatin A

1.4. Synthetic Efforts Towards Some Members of the Oroidin Family of Alkaloids

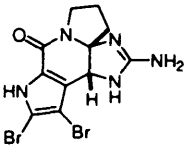
Over the last thirty years, numerous pyrrole-imidazole alkaloids with various structures and interesting biological activities have been identified from several species of *Agelasidae, Hymeniacidonidae,* and *Axinellidae.*[16] The versatility of the systems implicated in the biosynthesis of the oroidin-like pyrrole-imidazole alkaloids has consequently inspired many synthetic efforts. By finely tuning the reactivity of simple pyrrolic and 2-aminoimidazolic buildings blocks, many groups have achieved the elaboration of complex, naturally-occurring, pyrrole-imidazole structures.

1.4.1. Dibromophakellin and Related Alkaloids

Amongst the first known members of the pyrrole-imidazole alkaloid family, (-)-monobromophakellin and (-)-dibromophakellin ((-)-**14** and (-)-**15**, Figure 3) feature prominently. Each was isolated from the marine sponge *Phakellia flabellata* by Sharma and Burkholder.[17] Their structure was confirmed by X-ray analysis.[18,19] Interestingly, the optical isomer of **15**, (+)-dibromophakellin, was subsequently found in an extract of the sponge *Pseudoxaxinyssa cantharella.*[20] The structural assignment was also confirmed by X-ray analysis. A structurally related compound, (+)-dibromocantharellin (**16**, Figure 3) was also isolated from this sponge.[20]



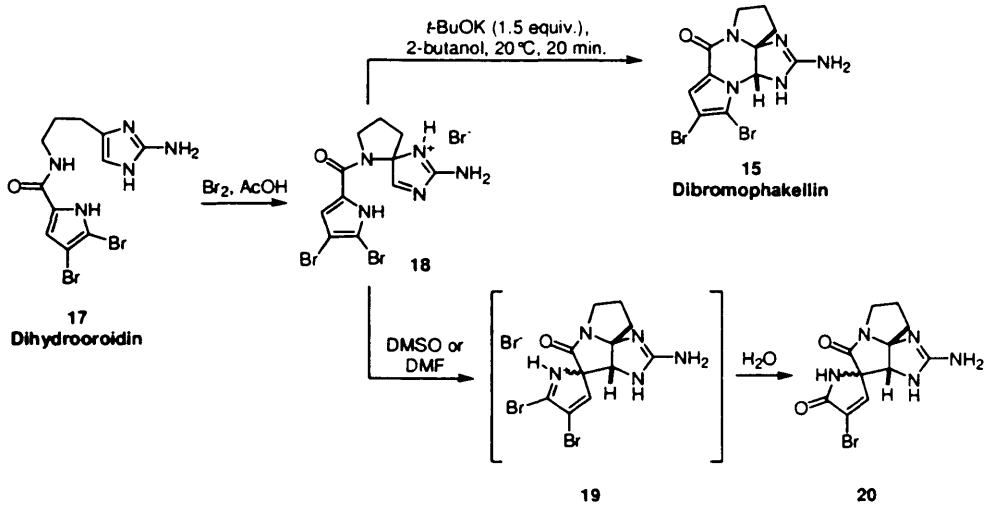
(-)-14; R = H (-)-Monobromophakellin
(-)-15; R = Br (-)-Dibromophakellin



(+)-16
(+)-Dibromocantharellin

Figure 3. Structure of dibromophakellin and dibromocantharellin

The first workers to establish a link between linear and cyclised pyrrole-imidazole alkaloids were Foley and Büchi.[21] They prepared racemic dibromophakellin by oxidative cyclisation of non-naturally occurring dihydrooroidin **17** (Scheme 4). They treated the hydrochloride salt of **16** with bromine in acetic acid to obtain the unstable hydrobromide salt **18** which, when reacted with a base, afforded racemic dibromophakellin **15**. Intriguingly, when **18** was dissolved in DMF or DMSO but without base, it underwent electrophilic substitution on carbon to furnish the dibromoiminium salt **19** which hydrolysed to the pyrrolinone **20**.



Scheme 4. The preparation of dibromophakellin by Büchi and Foley

The conditions for the oxidative cyclisation of **18** were later improved by Horne *et al*,[22] who used NBS in TFA and a Et_3N/THF (1:1) quench to access racemic dibromophakellstatin in nearly quantitative yield.

1.4.2. The Pyrroloazepinones

An important subdivision of the pyrrole-imidazole family of alkaloids is represented by the tricyclic natural products hymenin (**21**), odiline (**9**), hymenialdisine (**22**), and debromohymenialdisine (**23**, Figure 4). Each feature a fused bicyclic pyrrolo[2,3-c]azepin-8-one ring system that bears a 2-aminoimidazole appendage.

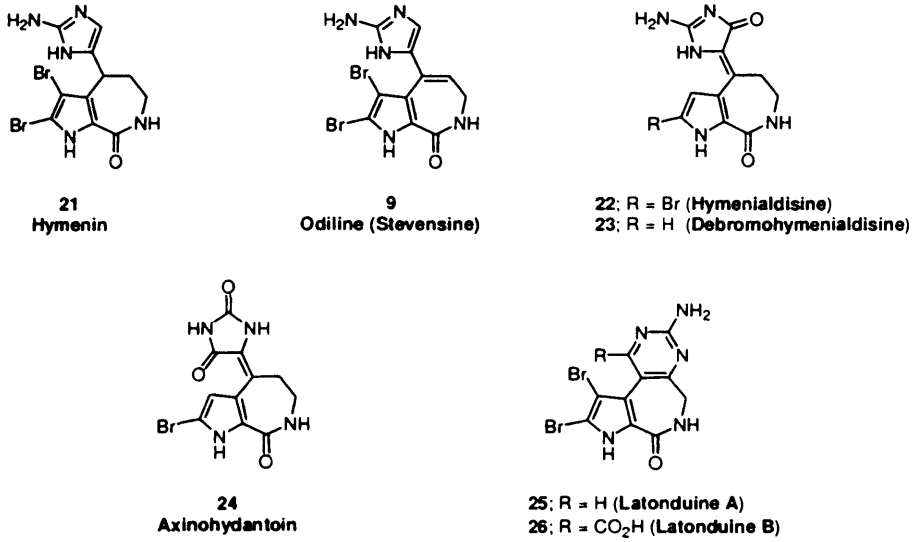


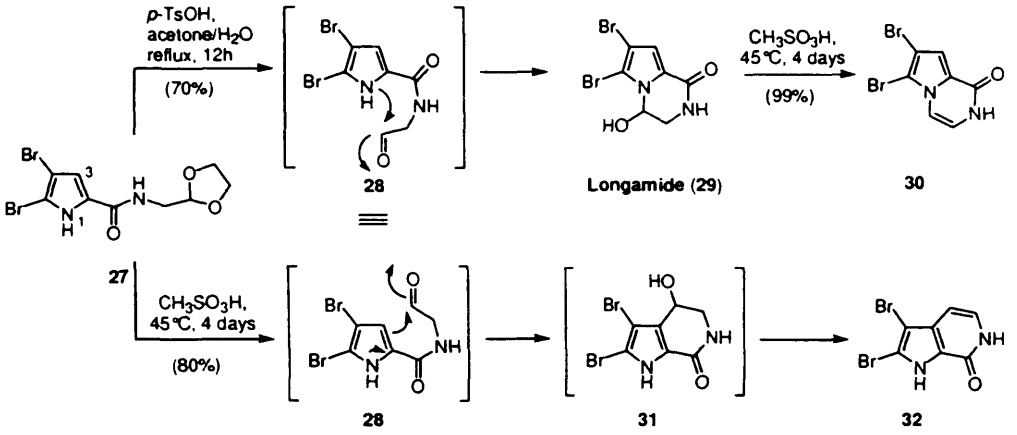
Figure 4. Structure of the pyrroloazepinone marine alkaloids and congeners

Debromohymenialdisine (**23**) was isolated from the Great Barrier Reef sponge *Phakellia flabellata* in 1980.[23] Subsequently, its brominated analogue, hymenialdisine (**22**) was extracted from the Mediterranean sponge *Axinella verrucosa* and from the Red Sea sponge *Acanthella aurantiaca*.[24] Both compounds were also isolated from the Okinawan sponge *Hymeniacidon aldis*.[12] Preliminary screening of hymenialdisine showed a moderate cytotoxicity against KB cancer cell lines *in vitro*.[24] The cytostatic and antineoplastic properties of hymenialdisine and debromohymenialdisine were later confirmed in the U.S. National Cancer Institute's murine P-388 lymphocytic leukemia test (ED_{50} = 2.0 μg/mL and 2.5 μg/mL, respectively).[25] Both hymenialdisine and debromohymenialdisine were reported to inhibit the G_2 DNA damage checkpoint (IC_{50} = 6 and 8 μM, respectively), and showed moderate cytotoxicity towards MCF-7 cells.[26]

Hymenialdisine was identified as a potent inhibitor of the mitogen-activated-protein-kinase-kinase-1 (MEK-1) with an IC_{50} of 6 μM.[27] MEK-1 belongs to the Ras-MAPK signalling cascade, which is involved in transmitting cellular signals from the cytosol to the nucleus, for the modulation of cell proliferation and differentiation.[28] More recently, hymenialdisine, was found to be a potent inhibitor of the pro-inflammatory cytokines, interleukin-2 (IL-2, IC_{50} = 2.5 μM), and tumour necrosis factor-α (TNF-α, IC_{50} = 1.4 μM).[29] These cytokines play an important role in the pathogenesis of rheumatoid arthritis and osteoarthritis. Their inhibition has been successful in clinical trials for the treatment of rheumatoid arthritis.[30] Further investigations of the anti-inflammatory properties of hymenialdisine have shown that it inhibits cytokine production through inhibition of the transcription factor NF-κB in U937 cells, a cell of monocyte lineage, at a concentration of 1-2μM.[31] Finally, hymenialdisine was identified as a potent inibitor of cyclin-dependant kinases such as CDK5 (IC_{50} = 28 nM), glycogen-synthase-kinase-3β (IC_{50} = 10 nM) and casein kinase 1 (CK1, IC_{50} = 35 nM).[32] Inhibition of these kinases have potential applications for treating neurodegenerative disorders such as Alzheimer disease.

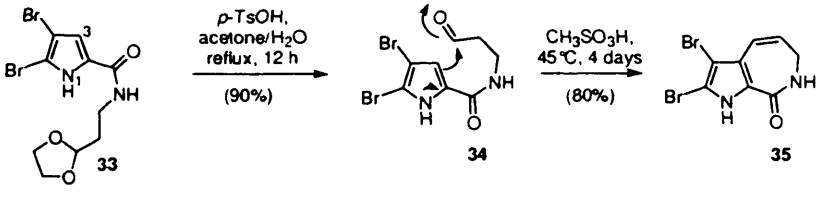
Hymenin (**21**) was isolated from the Okinawan sponge *Hymeniacidon sp.*[33] Preliminary studies have shown that this alkaloid is a competitive antagonist of the α-adrenoreceptors in vascular smooth muscle.[34] Odiline (also named stevensine, **9**) was simultaneously isolated from the sponge *Pseudoxaxinyssa cantharella* by de Nanteuil *et al*,[20] and from an unidentified sponge by Faulkner *et al.*[35] The related axinohydantoin (**24**) was isolated by Pettit from an *Axinella* sp. in 1990.[25] More recently, Andersen *et al.* published the isolation of two aminopyrimidines congeners, latonduines A and B (**25** and **26**), from the Indonesian sponge *Stylissa carteri*.[36] Their unprecedented heterocyclic skeleta contain a six-membered aminopyrimidine ring instead of the five-membered aminoimidazole ring common to the oroidin family, suggesting that ornithine could be their biogenetic precursor rather than the amino acids L-proline and L-histidine as proposed by Kerr *et al.*[9]

Chemical synthesis studies on these molecules have been carried out by the group of Horne.[37] They investigated the controlled regioselective intramolecular cyclisation of oroidin-like compounds (Scheme 5). Thus, when the pyrrolecarboxamidoacetal **27** was deprotected under standard conditions (*p*-TsOH, acetone/water), aldehyde **28** could not be isolated. It reacted immediately with N(1) position of the pyrrole to produce longamide (**29**), a metabolite isolated from the Caribbean sponge *Agelas longissima*.[38] This compound could then be dehydrated to form **30**. When the same acetal was treated with methanesulfonic acid, it underwent ring closure at the C(3) position of the pyrrole with concomitant dehydration to afford pyrrolopyridinone **32**.



Scheme 5. Preparation of cyclised analogues of odiline by regioselective cyclisation

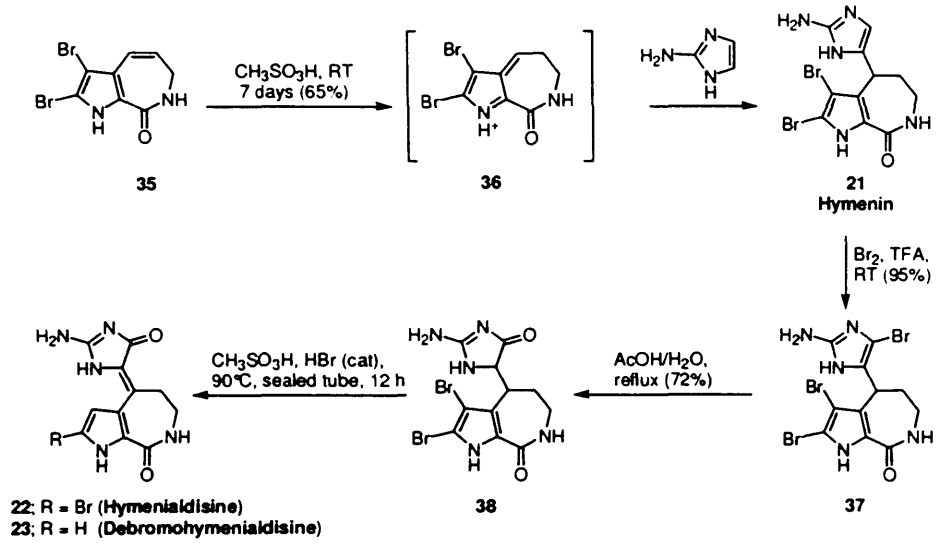
When the higher homologue **33** was submitted to the deprotection conditions used on **27**, aldehyde **34** was formed (Scheme 6). Moreover, while cyclisation to form the six-membered pyrrolopyrazine **30** occurred readily, the corresponding seven-membered ring closure was not observed. Cyclodehydration could be accomplished with methanesulfonic acid, which afforded the C(3) pyrroloazepine **35** exclusively.



Scheme 6. Preparation of the pyrroloazepine **35**

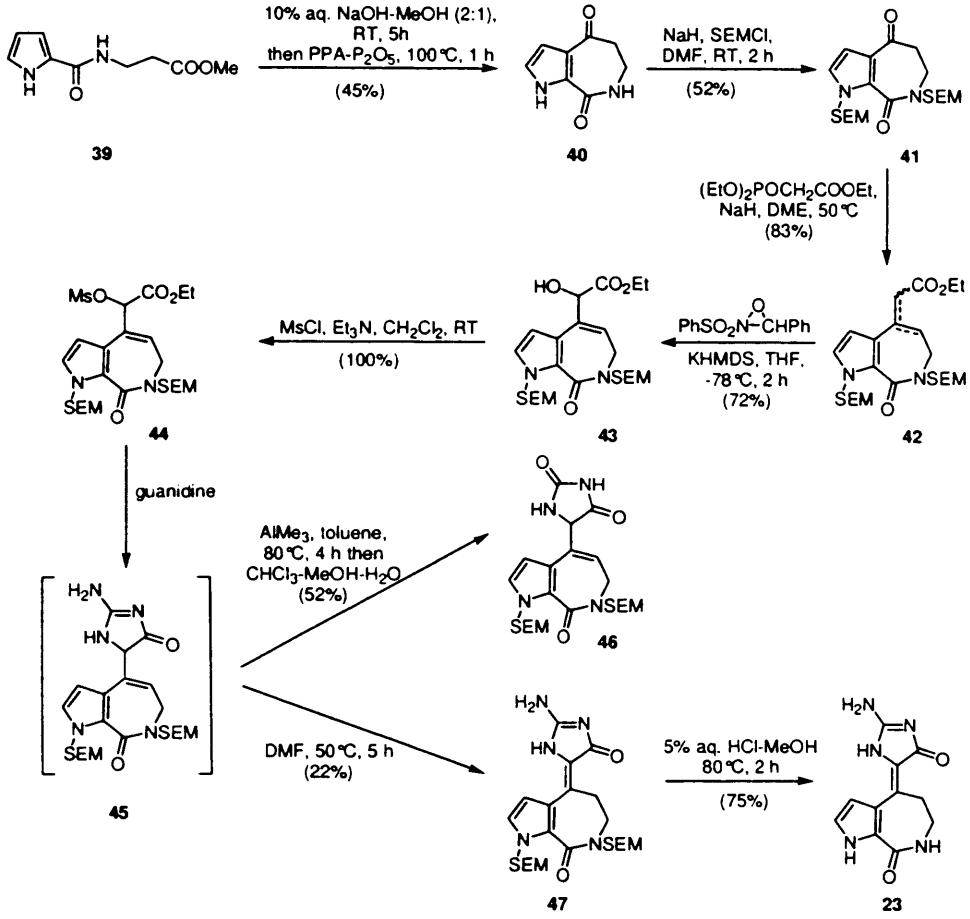
This compound could be further elaborated and coupled with an aminoimidazole moiety. In this capacity, Horne *et al.* reported the total synthesis of the two alkaloids hymenin (**21**, Figure 4) and hymenialdisine (**22**) in 1997.[39] Their synthesis was based on the preferential heterodimerisation of the two different heterocyclic units under acidic conditions. Thus, upon

exposure to methanesulfonic acid, pyrroloazepine **35** underwent protonation to give the putative azafulvene ion **36**, which reacted with 2-aminoimidazole to afford hymenin (**21**, Scheme 7). Oxidation of **21** with bromine in TFA, followed by mild hydrolysis with aqueous acetic acid afforded the imidazolone synthon **38** as a mixture of diastereoisomers. Regioselective debromination of the latter could be achieved by treating **38** with a catalytic amount of HBr in methanesulfonic acid. Under these conditions, HBr was generated *in situ* from **38** in a highly controlled manner that served to effect a selective protonation at the β-position of the pyrrole ring. Hymenialdisine (**22**) was produced in 33% yield, along with its debrominated analogue, debromohymenialdisine (**23**) in 27% yield. Those results are consistent with the fact that for bromination of 2-acylpyrrole systems, the β-position is generally the more reactive.[40] Furthermore, the favorable regioselective β debromination most likely accounts for the formation of the vast majority of monobromo series of marine alkaloids isolated to date.[16]



Scheme 7. Preparation of hymenin and hymenialdisine by Horne *et al.*

A successful total synthesis of debromohymenialdisine was achieved by Annoura *et al.*,[41] with complete control of the exocyclic olefin geometry. As illustrated below (Scheme 8), they started from linear pyrroloamide **39**. After hydrolysis of the ester, PPA-mediated cyclization of **39** afforded aldisin **40**. Protection of the nitrogen atoms with SEM groups yielded **41**. The Wittig-Horner reaction of the latter with ethyl diethylphosphonate/NaH afforded **42** as mixture of α,β and β,γ-unsaturated esters. Deprotonation of **42** with KHMDS at low temperature generated the ester anion, which was quenched with 2-benzenesulfonyl-3-phenyloxaziridine to give the α-hydroxy-β,γ-unsaturated esters **43**, as a single regioisomer. Mesylation of the alcohol function afforded **44** quantitatively.



Scheme 8. Preparation of debromohymenialdisine by Annoura *et al.*

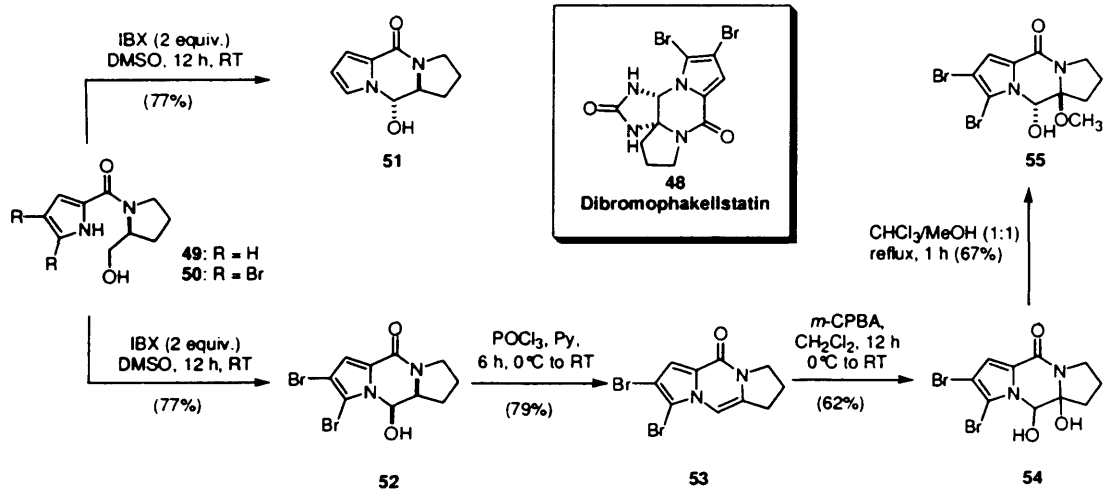
Reaction of **44** with guanidine (1.5 equiv.) in the presence of $AlMe_3$ in toluene at 80°C caused cyclisation to produce the hydantoin derivative **46**, presumably derived from hydrolysis of the initial guanidine adduct **45** during the work-up procedure. Despite many attempts with different conditions for the work-up (non-aqueous/basic), only hydantoin **46** could ever be obtained from this reaction. When **44** was treated with guanidine (5 equiv.) in DMF at 50°C, the cyclisation occurred with a shift of the double bond within the azepine ring system, in a stereospecific manner, to afford the desired olefin **47**. It seems that the isomerisation of the double bond into the conjugated system leads to stabilisation of the guanidine moiety by resonance effect, which can then be isolated without conversion to the corresponding hydantoin. Subsequent removal of the SEM protecting group cleanly afforded debromohymenialdisine **23**.

1.4.3. Dibromophakellstatin

A very interesting member of the oroidin family of pyrrole-imidazole alkaloids is (-)-dibromophakellstatin (**48**, Scheme 10), isolated by Pettit *et al.* from the Indian Ocean sponge

Phakellia mauritania.[42] This alkaloid exhibits potent cell growth inhibitory effects against melanoma SK-MEL-5 and colon KM20L2 cell lines (ED_{50} = 0.11 μg/mL for both cells).[42] Dibromophakellstatin possesses a unique array of functionality including a cyclic urea, a pyrrole carboxylic acid, a pyrrolidine, and a vicinal diaminal stereocentre packaged together in a highly compacted arrangement within a heteroatom-dense, tetracyclic structure.

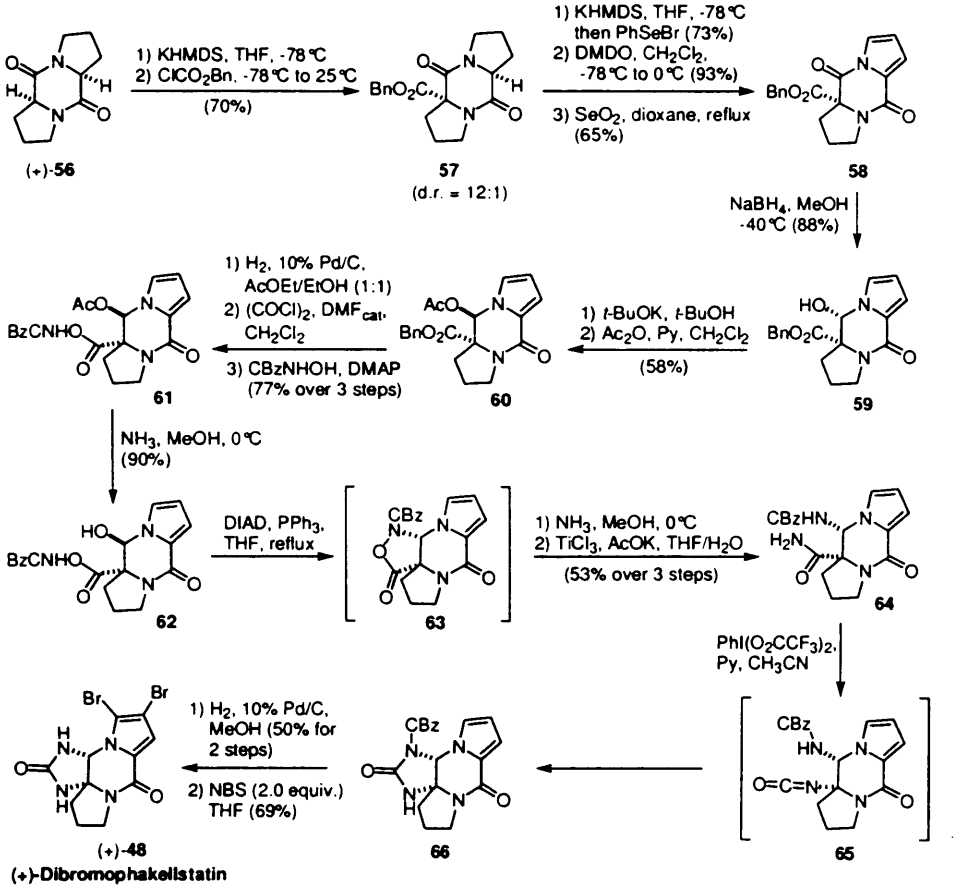
Synthetic efforts towards preparation of the dipyrrolopyrazinone core of dibromophakellstatin have been reported by Lindel *et al.* (Scheme 9), starting from pyrroloalcohols **49** and **50**.[43] Oxidation of the primary alcohol functionality in **49** and **50** to the corresponding aldehydes was achieved using IBX in DMSO, to prevent racemisation of the α-amino-aldehyde. The resulting aldehydes immediately cyclised to the *N,O*-hemiacetals **51** and **52**. While the dibrominated analogue gave the *syn* diastereoisomer, the non-brominated analogue **49** afforded only the *anti* diastereoisomer. Dehydration of **52** could be effected using phosphorus oxychloride to afford olefin **53**. Oxidation of the latter with *m*-CPBA yielded diol **54** whose relative stereochemistry could not be assigned. Treatment of **54** with excess methanol at reflux afforded exclusively **55**. The *trans* configuration in **55** was confirmed by X-Ray analysis.



Scheme 9. Preparation of the dipyrrolopyrazinone core of dibromophkellstatin

Recently, Romo *et al.* reported a total synthesis of (+)-dibromophakellstatin, the non-natural optical isomer (Scheme 10).[44] Their strategy was based on the desymmetrisation of the C_2-symmetric, proline-derived, diketopiperazine (+)-**56**,[45] obtained from naturally occuring L-proline in three steps. Acylation of the enolate derived from **56** with benzylchloroformate afforded diketopiperazine **57** in a highly diastereoselective fashion. This set the functionalised tricyclic core of dibromophakellstatin. Having fulfilled its role in controlling stereochemistry during acylation, the remaining H-containing α-stereocenter was removed by a selenation-selenoxide-elimination sequence which provided an intermediate pyrroline, which then

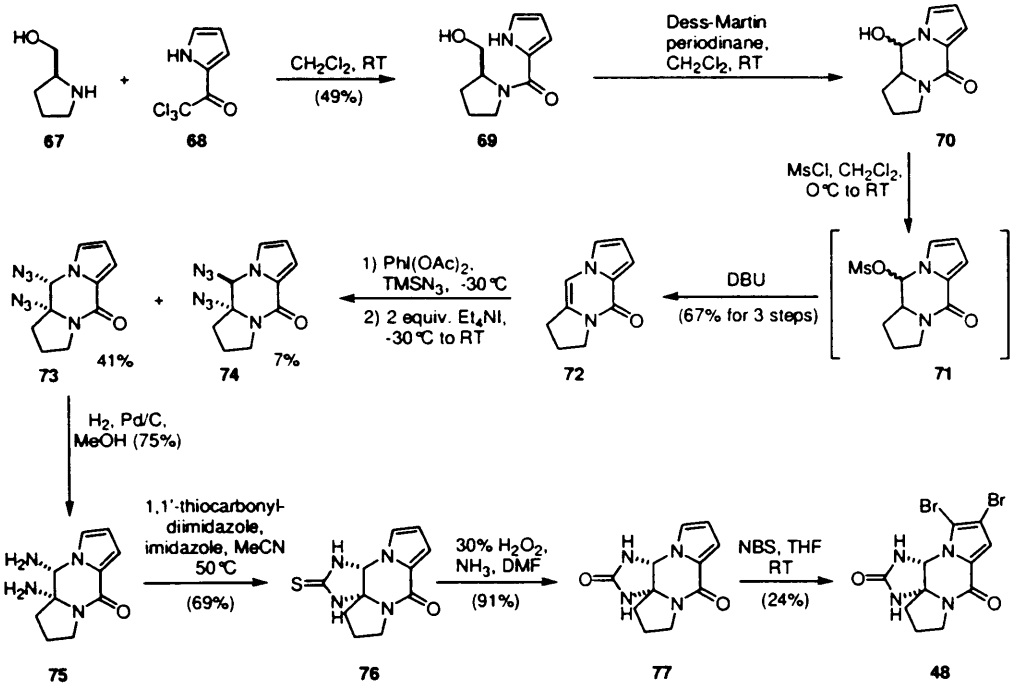
underwent further oxidation to the pyrrole, affording **58**. Diastereoselective reduction of the carbonyl group with sodium borohydride at low temperature afforded alcohol **59**. The regioselectivity observed in this reduction is noteworthy and is probably attributable to greater electrophilicity induced, in this amide carbonyl, by the electron-withdrawing α-carboxybenzyl group, and the occurrence of chelation during the reduction.



Scheme 10. Total synthesis of (+)-dibromophakellstatin

The newly-set carbinolamine stereocenter was then epimerised with potassium *tert*-butoxide, and protected as an acetate, affording **60**. The benzyl group was removed, and the resulting acid was coupled with benzyl *N*-hydroxycarbamate to furnish hydroxamate **61**. Aminolysis of the acetate followed by Mitsunobu coupling of the alcohol with the *N*-hydroxy ester afforded unstable tetracyclic intermediate **63**. This compound was immediately subjected to aminolysis, and N-O bond cleavage with $TiCl_3$, to deliver **64**. Hofmann rearrangement on the latter afforded the transient isocyanate **65** which was trapped *in situ* to give the tetracyclic urea **66**. Deprotection of the CBz group by hydrogenolysis followed by dibromination with 2 equiv. NBS afforded (+)-dibromophakellstatin ((+)-**48**).

A racemic synthesis of dibromophakellstatin was later reported by Austin and co-workers (Scheme 11).[46] Their strategy utilised a hypervalent-iodine mediated *syn*-diazidation to set the vicinal diamine appropriate for the installation of the urea ring system. This novel route started with construction of the 2,3-dihydrodipyrrolopyrazine core by coupling 2-pyrrolidinemethanol **67** with trichloroacetylpyrrole **68**. The resulting alcohol **69** was then oxidised with Dess-Martin periodinane to the corresponding aldehyde, which cyclised to the hemiaminal **70**.

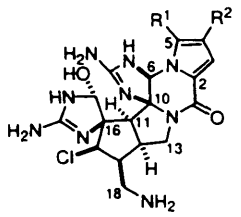


Scheme 11. Austin's route to (±)-dibromophakellstatin

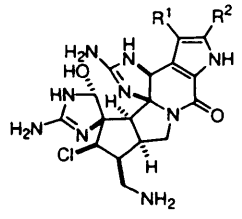
Mesylation of the alcohol in **70**, and elimination with DBU afforded dihydropyrrolopyrazinone **72** in 67% yield from **69**. Several methods were screened for the direct formation of a vicinal diazide functionality. It was found that *in situ* formation of the hypervalent iodine species $^-I(N_3)_2$ provided *syn*-diazide **73** as the main diastereomer (41%). Diazide **73** was converted into the corresponding diamine **75** by catalytic hydrogenation, and the thiourea ring was formed by treating **75** with thiocarbonyl-diimidazole. Conversion of thiourea **76** into urea **77** was efficiently achieved by peroxidation. Dibromination of **77** with NBS provided (±)-dibromophakellstatin, although in modest yields (24%), due to the presence of NBS-related side-products.

1.4.4. The Bisguanidines : Palau'amines and Congeners

Amongst the most intriguing members of the pyrrole-imidazole family of marine alkaloids are the palau'amines and styloguanidines (Figure 5). These hexacyclic bisguanidines possess a common, highly complex cyclopentane ring that is stereogenic at every carbon, including one quaternary spiro centre. Palau'amine (**78**) was isolated by Kinnel *et al.* in 1993, from the sponge *Stylotella agminata*, collected in the Western Caroline Islands.[47] It exhibited substantial antibiotic activity against Gram-negative and Gram-positive bacteria (it being active against *Bacillus subtilis* and *Staphylococcus aureus* at 10 µg/disk), as well as powerful cytotoxicity against tumour cell lines such as P-388 (IC_{50} = 0.1 µg/mL), A549 (IC_{50} = 0.2 µg/mL), HT-29 (IC_{50} = 2 µg/mL) and KB (IC_{50} = 10 µg/mL). Its most striking biological property is probably its immunomodulatory activity. In the mixed lymphocyte reaction, palau'amine showed an IC_{50} < 18 ng/mL, with a cytotoxicity against murine lymphocytes of only 1.5 µg/mL. Palau'amine is laevorotatory, but its absolute stereochemistry remains to be determined.



78: R^1, R^2 = H (**Palau'amine**)
79: R^1 = H, R^2 = Br (**Monobromopalau'amine**)
80: R^1, R^2 = Br (**Dibromopalau'amine**)

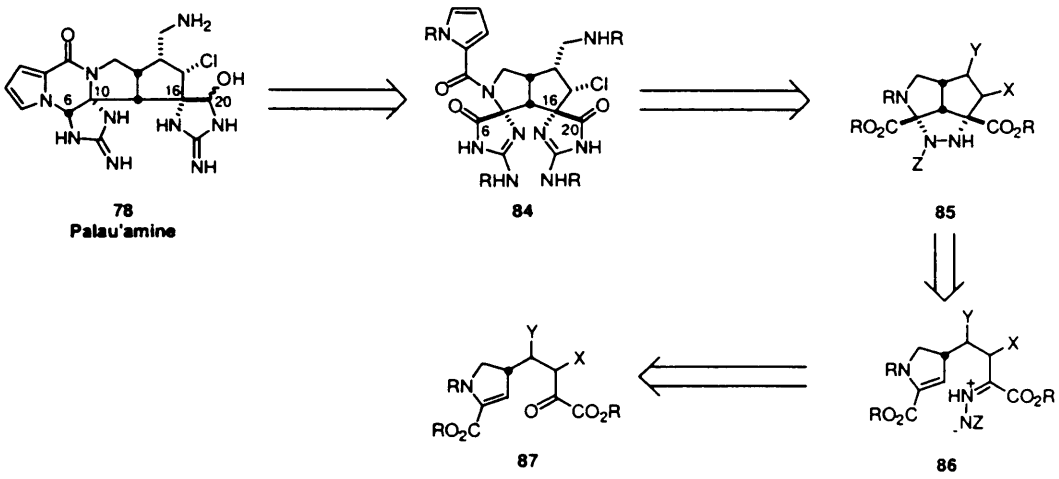


81: R^1, R^2 = H (**Styloguanidine**)
82: R^1 = H, R^2 = Br (**Monostyloguanidine**)
83: R^1, R^2 = Br (**Dibromostyloguanidine**)

Figure 5. Structure of the palau'amines and styloguanidines

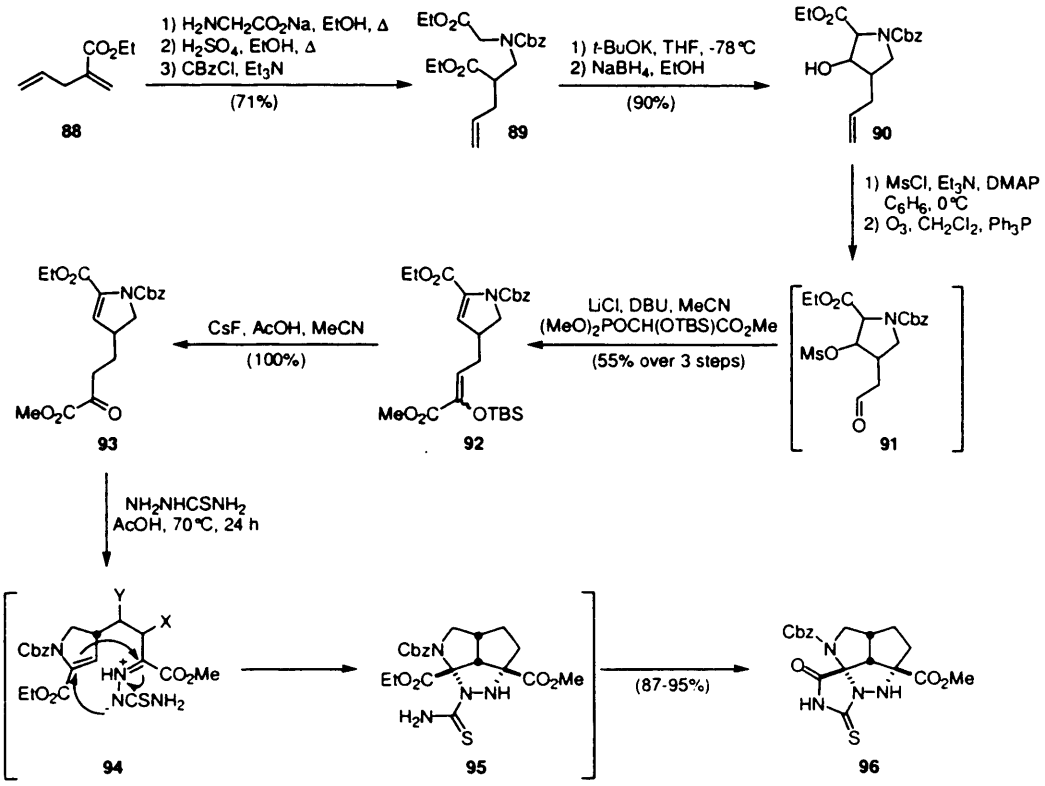
The isomeric alkaloids styloguanidines (**81-83**) were isolated two years later by Kato *et al.* from the sponge *Stylotella aurantinium*,[48] collected in the Yap Sea, along with palau'amine **78** and the dibrominated palau'amine analogues **79** and **80**. The styloguanidines are powerful chitinase inhibitors.

A concise route to an abbreviated tetracyclic core structure of palau'amine has recently been described by Overman *et al.*[49,50] In their retrosynthetic planning, a disconnection had been made at the linkage between C(6) and the 2-acylpyrrole unit to obtain the pentacyclic intermediate **84** (Scheme 12). This compound would be prepared from the hexahydrotriquinacene **85**, having the required stereochemistry at C(10) and C(20). The stereochemical relationship between the central *cis*-3-azabicyclo[3.3.0]octane core and the two spiroguanidines units in **85** would be established by an intramolecular cycloaddition on the azomethine imine **86**. In this pivotal step, the single stereocentre of **86** would direct the three additional stereocentres in **85**. Azomethine imine **86** would in turn be prepared from the corresponding α-ketoester **87**.



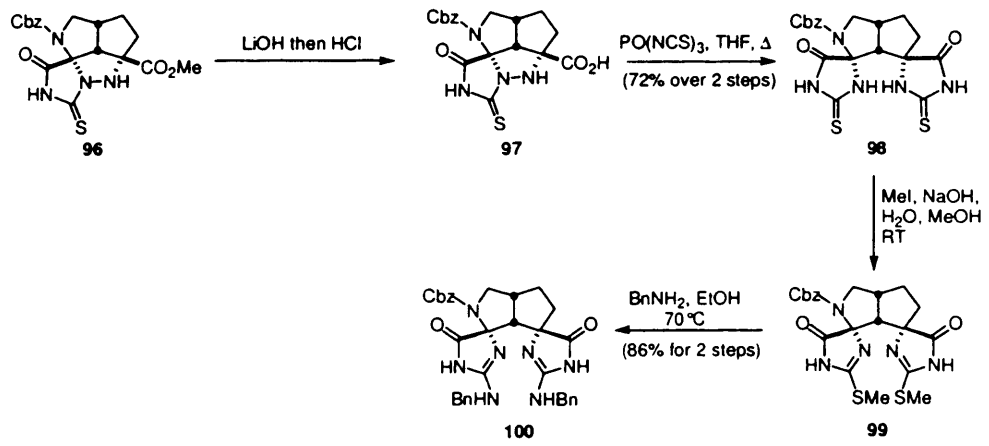
Scheme 12. Overman's retrosynthetic plan to palau'amine

Their synthesis of the abbreviated palau'amine core (compound **100** in Scheme 14) started with a conjugate addition of the sodium salt of glycine to ethyl (2-allyl)acrylate **88**; this was followed by esterification and *N*-Cbz protection to afforded **89** (Scheme 13). Dieckmann cyclisation of **89** and subsequent reduction of the β-ketoester product provided pyrrolidine **90**. *O*-Mesylation of **90** and direct ozonolysis of the mesylate afforded aldehyde **91**, which was submitted to a Wittig-Horner reaction with 2-(*tert*-butyldimethylsiloxy)-2-(dimethylphosphono)acetate to to give dihydropyrrole **92**. Desilylation of **92** with CsF provided racemic α-keto ester **93**. Reaction of **93** with thiosemicarbazide in acetic acid at 70°C delivered tetracycle **96** by a sequence of reactions that included an intramolecular cycloaddition to form **95**, followed by an acylation of the thiourea.



Scheme 13. Overman's route to an abbreviated analogue of palau'amine

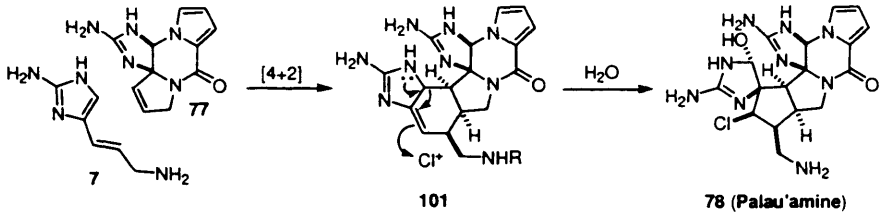
In order to fashion the second spirothiohydantoin, ester **96** was hydrolysed with lithium hydroxide, and the resulting acid was treated with phosphoryl isothiocyanate. This reagent also unexpectedly accomplished the reductive cleavage of the N-N bond. Finally, the desired bis-(acylguanidine) units were formed by sequential treatment of **98** with MeI and benzylamine.



Scheme 14. Completion of the synthesis of an abbreviated core structure of palau'amine

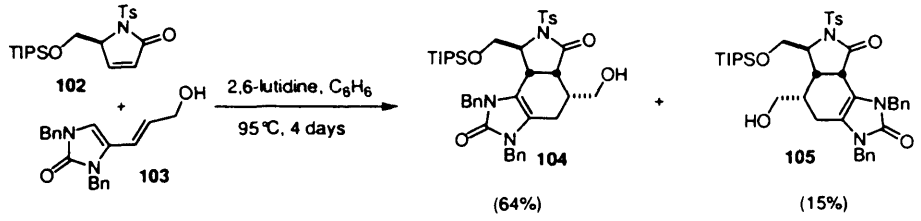
A route to the fully substituted cyclopentane core of the related axinellamine was reported by Carreira *et al.*[51] A biomimetic Diels-Alder approach to the palau'amine core, using 4-vinylimidazoles, was published by Lovely *et al.*[52] A transient N-O-linked Pauson-Khand strategy was proposed by Austin *et al.* for the synthesis of the deschloro carbocyclic core of the palau'amines and styloguandines.[53]

More recently, Romo *et al.* reported the preparation of the spirocyclic core of palau'amine,[54] following a biosynthetic pathway suggested by Kinnel.[55] In this proposal (Scheme 15), a Diels-Alder reaction would occur between dehydrophakellin **77**, an unknown metabolite related to dibromophakellin (**15**, Scheme 4), and a known metabolite, 2-amino-1-(2-aminoimidazolyl)prop-1-ene (**7**), isolated from the sponges *Teichaxinella morchella* and *Ptilocaulis walpersi*.[56] A subsequent chlorination involving a chloroperoxidase, would then initiate a pinacol-like 1,2-shift/ring contraction to deliver the spirocycle found in **78** after capture of the resulting iminium ion by water.



Scheme 15. Proposed biosynthetic pathway to palau'amine

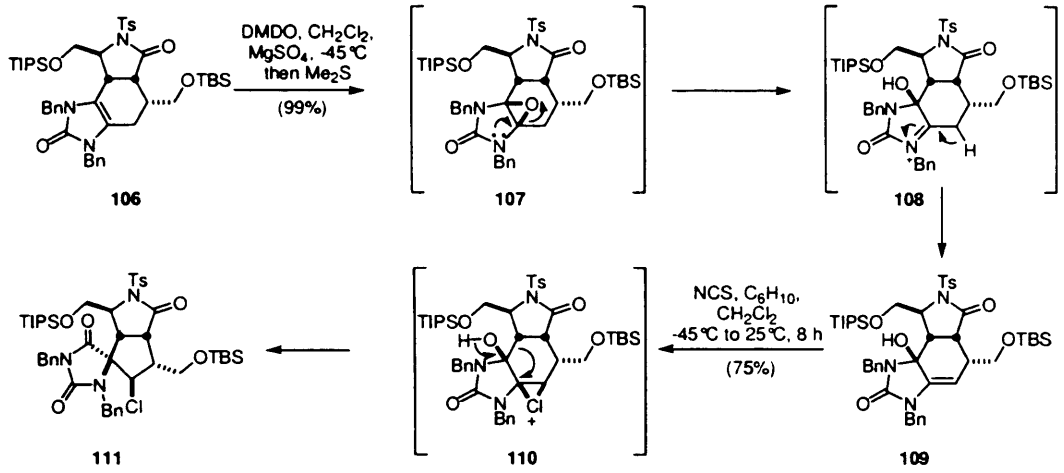
Following this proposal, Romo *et al.* investigated the Diels-Alder reaction between imidazolone **102** and pyroglutamic derived lactam **103**. Reaction of these two compounds in benzene for 4 days afforded the desired *endo* cycloadduct **104** (enantiomeric excess > 95%), along with the minor regioisomer **105** (Scheme 16). However, a migration of the double bond occurred during the course of the Diels-Alder reaction to regenerate the imidazolone ring.



Scheme 16. Diels-Alder reaction *en route* to the palau'amine core structure

After protection of the alcohol in **104** with a TBS group, they investigated the 1,2-shift/ring-contraction sequence. Careful treatment of imidazolone **106** with dimethyldioxirane (DMDO) afforded diastereoselectively alcohol **109** (Scheme 17). Presumably, the mechanism of this

reaction involves initial epoxidation of the double bond to form **107**, epoxide ring-opening to give the iminium ion **108**, and deprotonation to produce **109**. An intermolecular chlorination from the convex face of carbinol-urea **109** thereafter promoted the desired suprafacial 1,2-alkyl shift to afford the chlorinated hydantoin **111**. However, this product was epimeric at the C(17) chlorine-bearing atom in palau'amine. Further investigations will be necessary to control the regioselectivity of the chlorination process. A substrate-directed chlorination by the pendant alcohol fonction in **109** is being investigated to access the cyclopentane stereochemistry of palau'amine.[54]



Scheme 17. Formation of the spirocyclic core of palau'amine

1.4.5. Sceptrin and Analogues

Sceptrin (**112**, Figure 6) is a novel structure that was originally isolated from *Agelas sceptrum*,[57] and subsequently from the Caribbean sponge *Agelas conifera*.[58] Sceptrin was also discovered in the Indopacific sponge *Agelas nakamurai*,[59] along with debromosceptrin (**113**), and a new structure, nakamuric acid (**114**). Sceptrin shows interesting antimicrobial and antifungal activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Candida albicans*.[58]

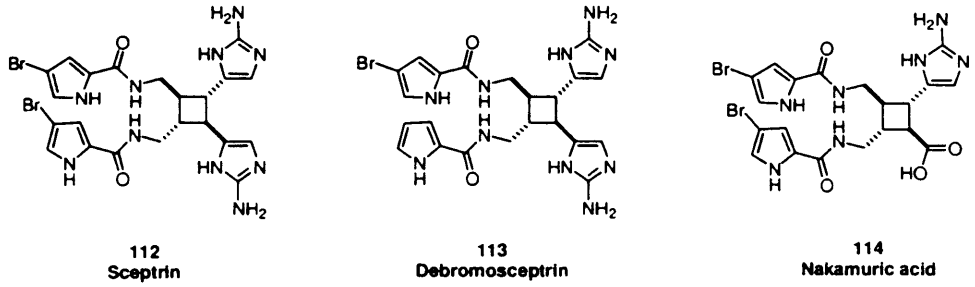
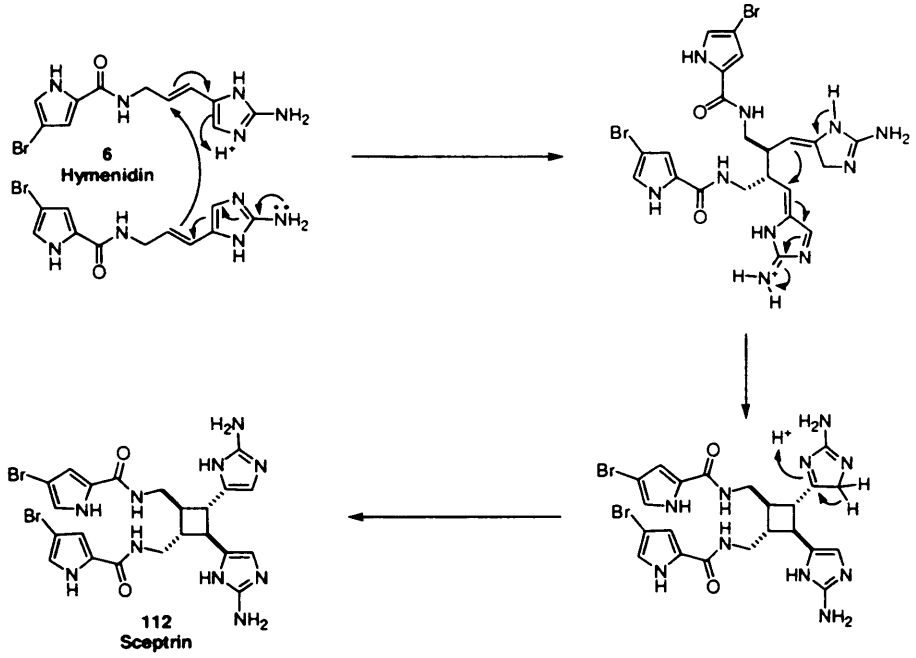


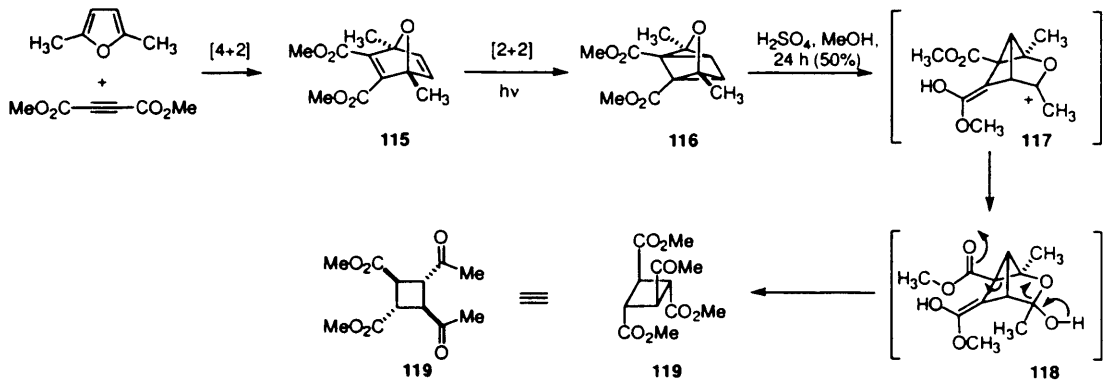
Figure 6. The sceptrin family of alkaloids

Sceptrin can be considered as a dimer of debromooroidin (hymenidin, **6**) by a formal [2+2] cycloaddition reaction. Although the photochemical reaction would be allowed, any attempts to prepare sceptrin by the photodimerisation of debromooroidin have so far been unsuccessful. The biosynthesis of sceptrin is unlikely to occur by photodimerisation since there is not enough light at the depth where the sponge was found (-20 m to –30 m), and sceptrin is chiral ($[\alpha]_D$ –7.4° in methanol), while debromooroidin is not. An alternative biogenetic pathway has been suggested by Rinehart and co-workers,[58] which involves ionic dimerisation (Scheme 18).[58]



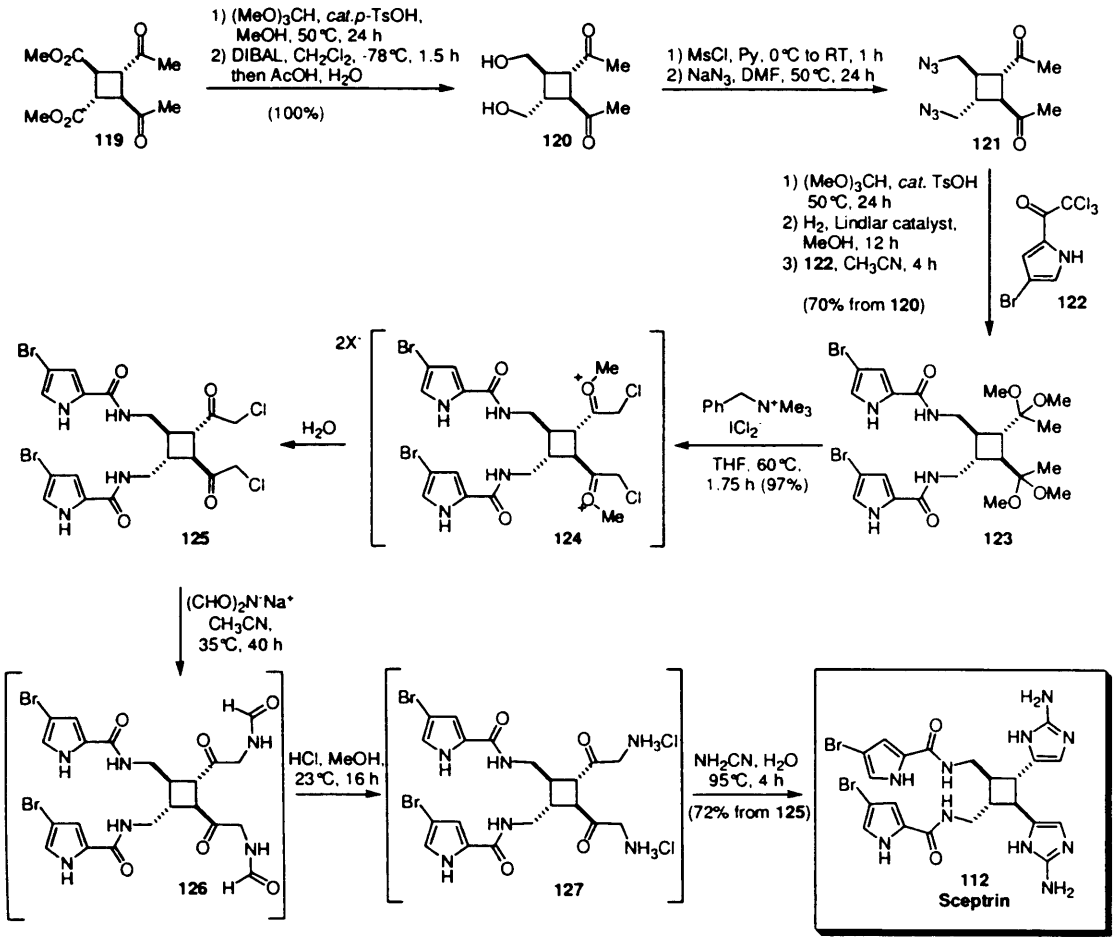
Scheme 18. A putative biogenetic pathway for sceptrin

Sceptrin remained a prominent unanswered synthetic challenge until Baran *et al.* reported the first total synthesis of (±)-sceptrin in 2004.[60] Their route to **112** is based on the known acid-promoted rearrangement of 3-oxaquadricyclane **116**,[61] to form the cyclobutane core of sceptrin. Cyclane **116** was prepared by Diels-Alder reaction cycloaddition of 2,5-dimethyl furan and dimethyl acetylene dicarboxylate, followed by photoirradiation.[62] The conversion of **115** to cyclobutane **119** probably occurs *via* formation of carbenium ion **117**, which is stabilised by both an α methyl and an α oxygen (Scheme 19). Addition of water yields hemiacetal **118** which rearranges to form the *trans,trans,trans*-cyclobutane **119**.



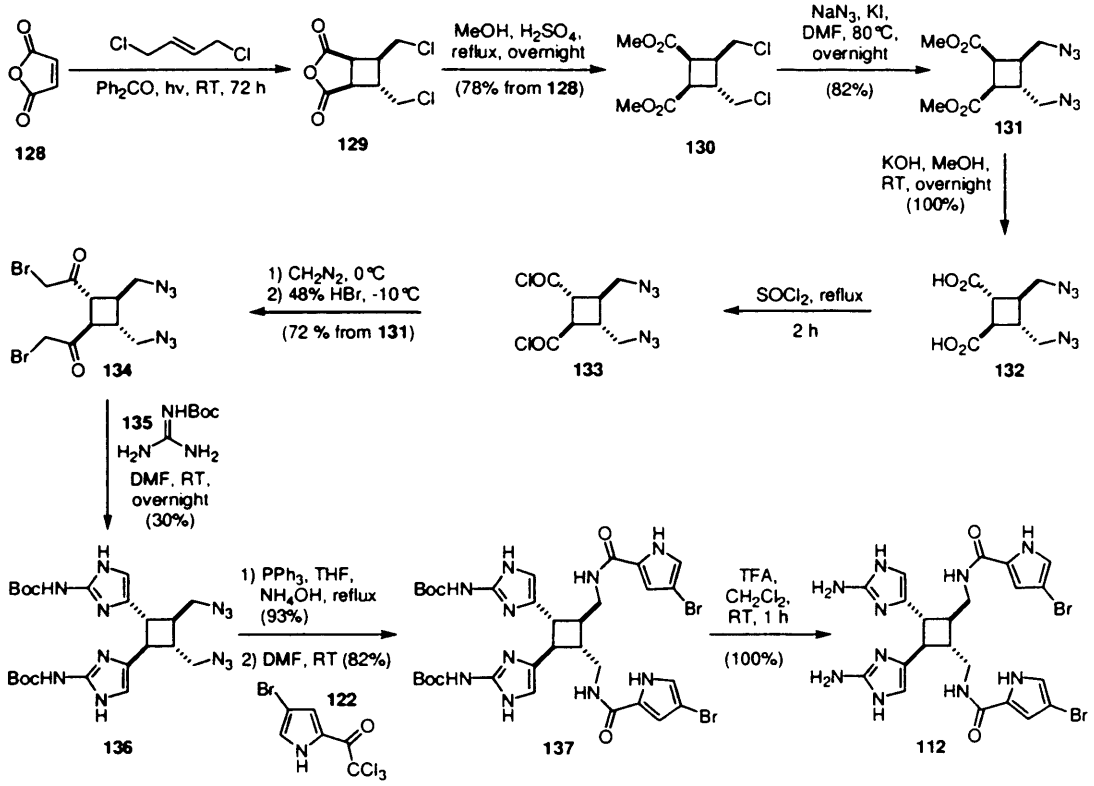
Scheme 19. Rearrangement of 3-oxaquadricyclane **116**

Next, diester **119** was converted to the corresponding diol **120** (Scheme 20) by protection of the ketone as the dimethylketal, reduction of the diester to the corresponding diol, and acidic work-up. Conversion of **120** to diazide **121** was achieved by mesylation and nucleophilic displacement with azide ion. Reprotection of the diazide as the dimethylketal was necessary to avoid scission of the sensitive cyclobutane ring in the ensuing catalytic hydrogenation and acylation steps. Chemoselective halogenation of **123** to secure bis-α-chloroketone **125** was achieved using benzyltrimethylammonium dichloroiodate. The reaction is thought to proceed *via* oxonium ion **124** since the ketone analogous to **123** does not provide **125** under the same conditions. Next, treatment of **125** with sodium diformylamide gave **126**, which afforded the bis-aminoketone **127** after acidic work-up. Treatment of the latter with cyanamide formed the two aminoimidazole ring systems, completing the first total synthesis of (±)-sceptrin in 24% overall yield from methylacetylene dicarboxylate.



Scheme 20. Total synthesis of sceptrin

Another synthesis of racemic sceptrin was subsequently reported by Birman *et al.*[63] In their route (Scheme 21), they took advantage of the known photocycloaddition of maleic anhydride to *trans*-1,4-dichloro-2-butene to produce adduct **129**. The latter was converted to the dimethyl ester **130**, which was treated with sodium azide to furnish **131**. Hydrolysis of the diester to the corresponding diacid occurred with epimerisation to the more thermodynamically stable all-*trans* diacid **132**. This compound was then converted into bis-bromomethylketone **134**. Treatment of **134** with *tert*-butoxycarbonylguanidine **135** set the 2-aminoimidazole moieties, affording **136** in modest yields (30%). Reduction of the azido groups, followed by acylation with **122** produced **137**. Removal of the Boc groups with TFA afforded sceptrin as its bis-trifluoroacetate salt.



Scheme 21. Birman's route to (±)-sceptrin

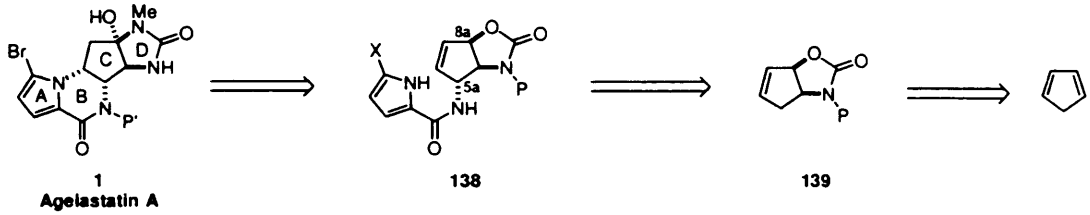
Novel alkaloids are continuously isolated from various marine sponges. Amongst the latest reported feature the mukanadins A-C,[64] sventrin,[65] the slagenins A-C.[66]

1.5. Previous Synthetic Efforts Towards Agelastatin A

1.5.1. Weinreb's Racemic Total Synthesis of Agelastatin A

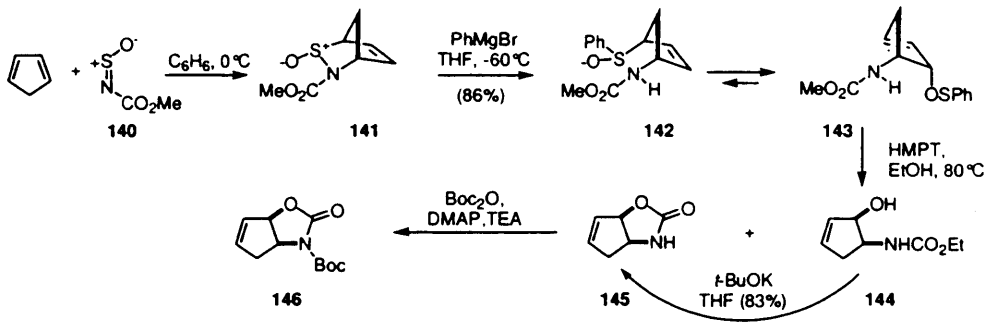
The first total synthesis of (±)-agelastatin A was reported by Weinreb *et al.* in 1999.[67,68] Their approach used cyclopentadiene as the source of the highly functionalised cyclopentane ring of the natural product (Scheme 22). They expected that the hydroxy urea center in **1** would be controlled by the fact that the *cis*-configuration of the C-D ring-junction would be more favourable than the alternate *trans* arrangement which would be prohibitively strained. In their plan, cyclopentadiene was to be converted into oxazolidinone **139**. The C(5a) nitrogen would then be introduced regioselectively on the convex face of **139** to give **138**. The pyrrole A-ring would be attached to this nitrogen by acylation. Given the sensitivity of the C(1) bromide in agelastatin A (it can be reductively removed by treatment with sodium hydride), a synthetic

equivalent of this substituent was deemed esential. A palladium-promoted cyclisation would then be used to ensure the BC ring junction formation.



Scheme 22. Weinreb's retrosynthetic plan for agelastatin A

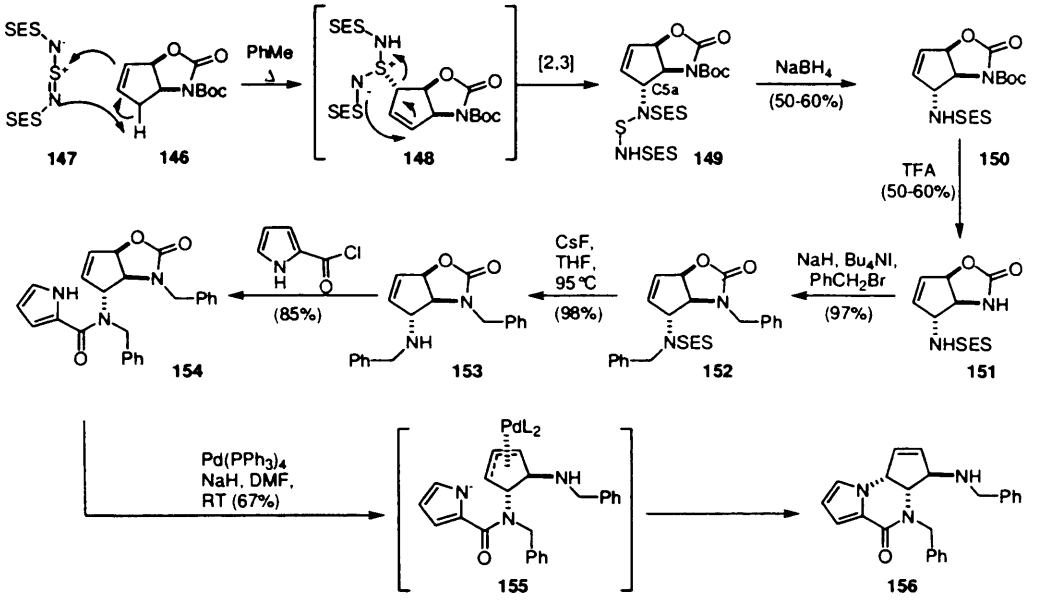
Hetero Diels-Alder methodology was used to construct the bicyclic carbamate **145** (Scheme 23). Thus, condensation of cyclopentadiene with *N*-sulfinyl methyl carbamate **140** as the dienophile in benzene at 0°C afforded cycloadduct **141**. As this product was prone to the *retro* Diels-Alder process, it was immediately reacted with phenyl magnesium bromide to produce the stable allylic sulfoxide **142**. This compound was then heated with HMPT in ethanol to promote a [2,3]-sigmatropic rearrangement *via* sulfenate ester **143** to afford a 1:1 mixture of the desired olefinic oxazolidinone **145** and the uncyclized hydroxy ethyl carbamate **144**. The latter could be converted to **145** with potasium *tert*-butoxide in high yield. The oxazolidinone nitrogen was then protected with a Boc group to produce **146**.



Scheme 23. Preparation of the cyclic carbamate

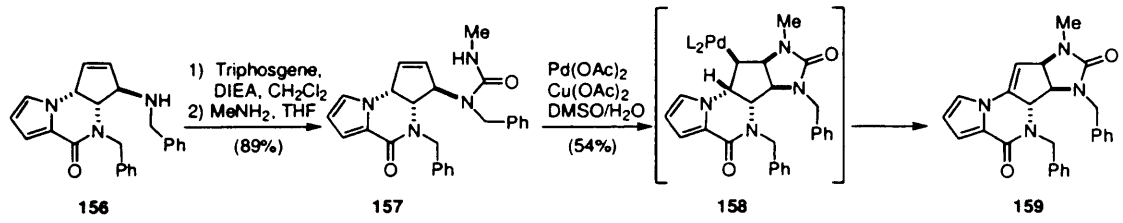
The C(5a) nitrogen was then introduced into carbamate **146** by a Sharpless-Kresze allylic amination (Scheme 24), which proceeds *via* preliminary ene reaction between **146** and the SES-protected *bis*-sulfodiimide **147** and a [2,3]-sigmatropic rearrangement. The resulting product **149** was then reduced with sodium borohydride to obtain the allylic sulfonamide **150**. The SES (β-trimethylsilylethanesulfonyl) protecting group in **147**, originally developed by Weinreb,[69,70] was used as an alternative to *p*-toluenesulfonyl and methyl carbamate groups, because they thought it would be more easily removed by fluoride ion later in the synthesis.

The Boc group in **150** was removed with TFA, and the resulting sulfonamide **151** was made less polar by di-*N*-benzylation, producing **152**. The SES group was cleaved off with caesium fluoride in hot THF, and the free amine was acylated with pyrrole-2-carboxylic acid chloride, securing **154**. Palladium-promoted cyclization of **154** led to the tricyclic alkene **156**. It is likely that this reaction proceeds *via* a π-allylpalladium intermediate **155** formed with inversion of configuration from carbamate **154**. Alkylation of the pyrrole nitrogen in **155** occurred with the expected *cis* selectivity, because the the *trans*-fused 6,5-ring system would be highly strained.



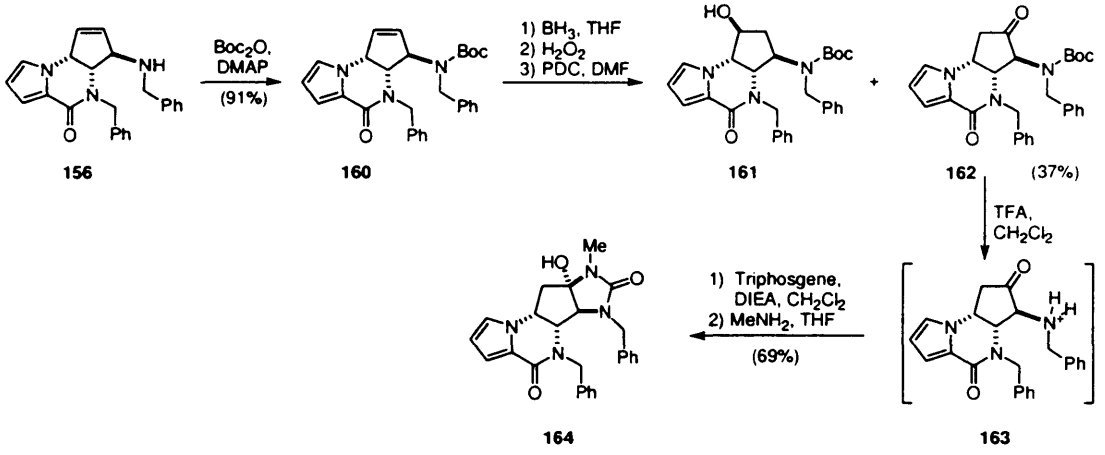
Scheme 24. Introduction of the C(5a)-N bond and first attempts at forming the ABC ring system

Palladium-based chemistry was also used in a preliminary attempt to form the D ring of agelastatin A (Scheme 25). Thus, amine **156** was converted to *N*-methyl urea **157**, which was treated with a catalytic amount of palladium acetate and copper acetate as the stoichiometric reoxidant to produce the tetracyclic ene urea **159**. This reaction was thought to occur *via* a syn addition of the palladium(II) and the urea nitrogen to the olefinic double bond in **157**. A subsequent reductive β-hydride elimination from the less hindered convex face of the tricycle led to the olefinic urea **159**. Since hydration of **126** would not afford the correct C/D ring functionality, this route was eventually abandoned.



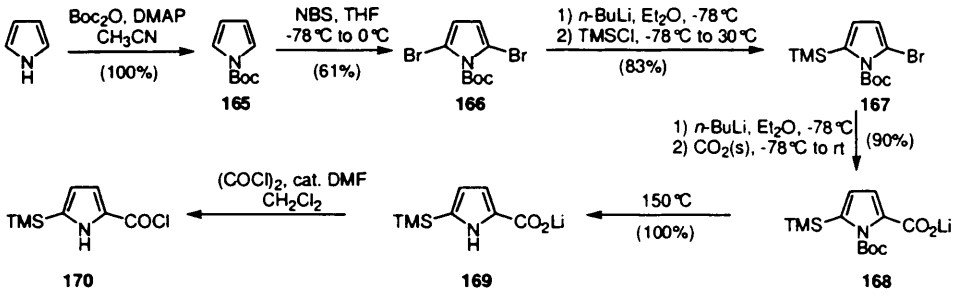
Scheme 25. Preliminary attempts at forming the D ring of agelastatin A

An alternative strategy was then envisioned, in which the olefinic double bond in tricyclic **156** would be selectively functionalised (Scheme 26). After conversion of **156** to the Boc derivative **160**, the latter was hydroborated with diborane, to give after treatment with hydrogen peroxide, a mixture of alcohols that were immediately oxidized with pyridinium dichromate. The desired ketone **162** was obtained in 37% yield, along with what was thought to be the undesired alcohol **161**. Unfortunately, the regioselectivity of this reaction could not be improved. However, the Boc group in **162** could be readily cleaved with TFA to afford α-amino ketone **163** which apparently did not self-condense. It did however readily cyclise upon treatment with triphosgene followed by addition of methylamine. Whilst this produced the correctly functionalised tetracyclic core of agelastatin A **164,** removal of the two *N*-benzyl protecting groups from **164** was problematical. Therefore, this strategy had to be modified.



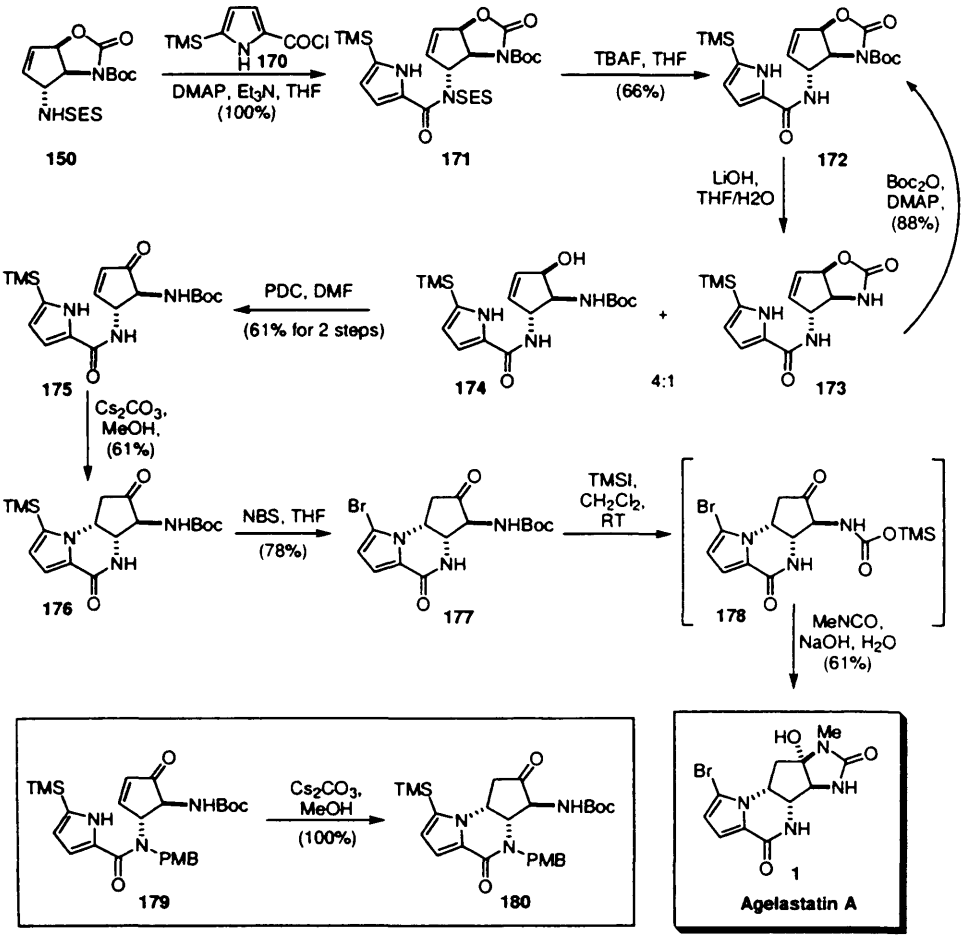
Scheme 26. Formation of the tetracyclic core of agelastatin A by hydroboration

At this stage, a synthetic equivalent of 5-bromopyrrole-2-carboxylic acid was developed. Due to the sensitivity of the bromine group in the natural product, it was thought that a 2-trimethylsilyl-derivative such as **170** should be used instead. This grouping should efficiently promote a regioselective *ipso* substitution with bromine at a later stage. It should not be forgotten that direct bromination of pyrrole bearing an α-carbonyl group (ester, acid, aldehyde) often provides a mixture of the 4- and 5-substituted bromopyrrole.[40] Thus, pyrrole was protected with a Boc group following the procedure of Grehn and Ragnarsson to obtain **165**,[71] which was then cleanly dibrominated with NBS to afford **166**.[72] This derivative was then monometallated with *n*-butyllithium, and then monosilylated with chlorotrimethylsilylane, following the procedures previously reported by Cava *et al.*,[73] producing **167**. This compound could be lithiated again, and then carboxylated with solid carbon dioxide to prepare **168**. Decarboxylation was effected cleanly by heating this compound neat at 150°C. The acid chloride **170** was then prepared from **169** by treating it with oxalyl chloride in the presence of a catalytic amount of DMF in dichloromethane.



Scheme 27. Preparation of the pyrrole acid chloride **170**

A new strategy was now devised to access the tetracyclic ring system of agelastatin A which involved an intramolecular conjugate addition of the pyrrole nitrogen in **175** to the cyclopentenone (Scheme 28). Thus, previously obtained sulfonamide **150** could be acylated with acid chloride **170** in quantitative yield, securing **171**. The SES group was removed from **171** with TBAF in THF, yielding pyrroloamide **172**. Hydrolysis of the oxazolidinone moiety in **172** occurred chemoselectively to give an inseparable 4:1 mixture of **174** and **173**. Oxidation of the mixture with PDC afforded the desired unsaturated ketone **175** as well as recovered oxazolidinone **173.** The latter could effectively be recycled by acylation with Boc_2O. Conjugate addition occurred after **175** was treated with caesium carbonate in methanol; the tricyclic ketone **176** was formed in 61% yield. It should be noted here that a similar reaction performed on the PMB-protected analogue **179** yielded the cyclized ketone **180** in 100% yield. It is reasonable to assume that the presence of substituent on N(5) promotes a population of the required amide rotamer.

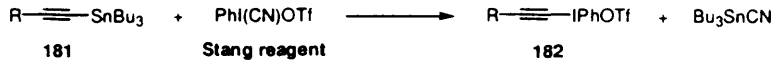


Scheme 28. Completion of Weinreb's total synthesis of agelastatin A

Next, replacement of the silyl group in **176** with NBS cleanly produced bromopyrrole **177**. Removal of the Boc group from **177** with TFA produced a product which rapidly dimerised, even in dilute solution. Weinreb finally reported that the Boc group could be effectively cleaved from **177** with excess trimethylsilyl iodide at room temperature. Subsequent addition of methyl isocyanate and dilute aqueous NaOH led to (±)-agelastatin A in 61% yield. It is likely that this process involved formation of a silyl carbamate such as **178**. This intermediate was then converted to the free amine, which was trapped by the methyl isocyanate to effect the annulation of the D ring. This first total synthesis of racemic agelastatin A proceeded in 14 steps and 7% overall yield.

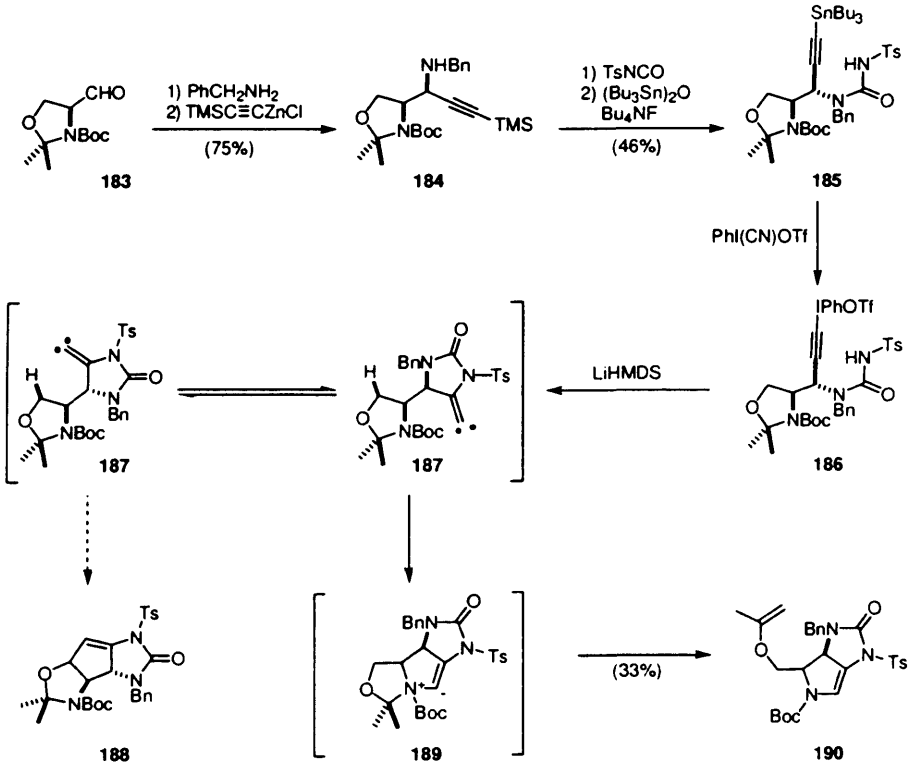
1.5.2. Feldman's Enantioselective Route to (-)-Agelastatin A

In 2002, Feldman and co-workers reported the first enantioselective total synthesis of (-)-agelastatin A.[74,75] Their strategy stemmed out of some original work of Oichiai,[76] who showed that alkynyliodonium salts were competent electrophiles when partnered with soft nucleophiles. Such conditions lead to highly reactive alkylidenecarbenes, which can insert into an unactivated C-H bonds five atoms removed from the carbenic centre to furnish functionalized cyclopentenes with retention of stereochemistry at the newly formed stereogenic center. Alkynyliodonium salts such as **182** (Scheme 29) can be prepared from an alkynylstannane precursor like **181** using PhI(CN)OTf, a phenyliodonium transfer reagent recently developed by Stang.[77]



Scheme 29. Preparation of alkynyliodonium salts

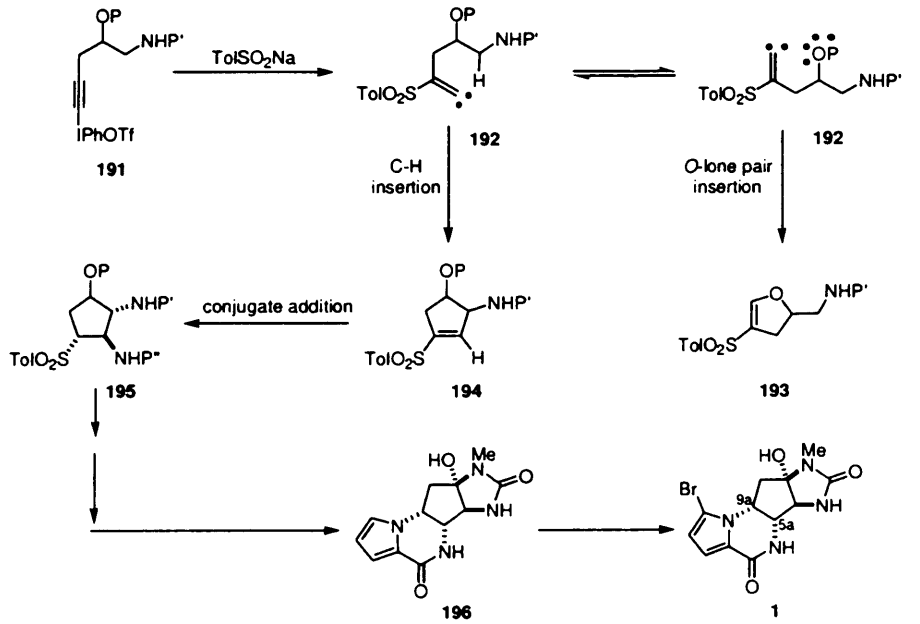
Feldman's first plan for obtaining (-)-agelastatin A (Scheme 30) envisioned using cyclopentene **188** as a key intermediate. The latter would be obtained from alkynyliodonium salt **186** *via* alkylidene carbene **187**.[78] Accordingly, the cyclisation precursor **185** was prepared from Garner's aldehyde **183** by a Fujisawa chelation-controlled imine addition reaction of trimethylsilylacetylene zinc chloride.[79]



Scheme 30. Feldman's first generation route to (-)-agelastatin A

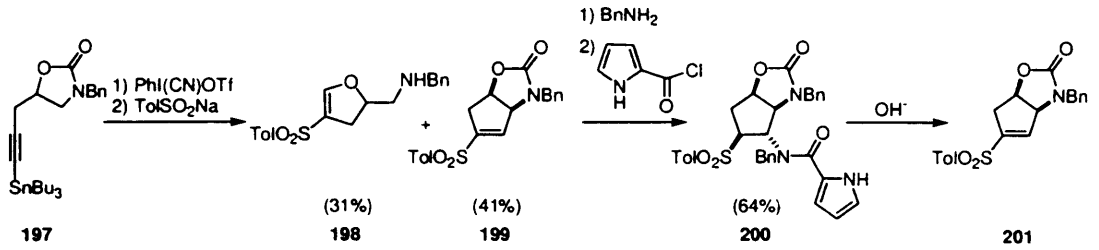
This methodology delivered the required *syn* diamine arrangement. Acylation of the amine **184** with tosyl isocyanate was followed by a Buchwald Si/Sn exchange reaction,[80] affording tributylstannane **185**. The latter was converted to the corresponding iodonium salt **186** using the Stang reagent. It was hoped that the reactive carbene species **187**, formed upon treatment of alkynyl iodonium salt **186** with LiHMDS, would deliver the bicyclic alkene-containing product **188** by insertion of the carbene into the adjacent C-H bond. Unfortunately, dihydropyrrole **190** was obtained instead. This result indicated that the putative alkylidenecarbene **187** added to the Boc carbamate's lone pair rather than inserting into the 1,5 C-H bond, forming an ylide **189** that rearranged to **190**. In light of the difficulties encountered in the regioselectivity of the carbene insertion reaction, this route was eventually abandoned.

A new strategy was thereafter devised, that revolved around generating the alkylidene carbene **192** from alkynyliodonium salt **191** by treatment with sodium toluenesulfinate (Scheme 31). It was hoped that the desired 1,5 C-H insertion would occur to give the cyclopentene **194**, although it was recognised that this reaction might compete with the carbene insertion into the γ-O lone pair to provide dihydrofuran **193**. *A priori*, the outcome of the carbene insertion reaction was therefore not guaranteed. The toluenesulfonyl grouping in **194** would then be used to trigger the conjugate addition of a nucleophilic amine group to C(5a) (agelastatin A numbering) to form **195**. The same sulfone unit would later be used as a leaving group to permit attachment of the pyrrole group at C(9a) to afford **196**. Finally, a selective bromination of the pyrrole ring at C(1) would provide the natural product **1** from **196**.



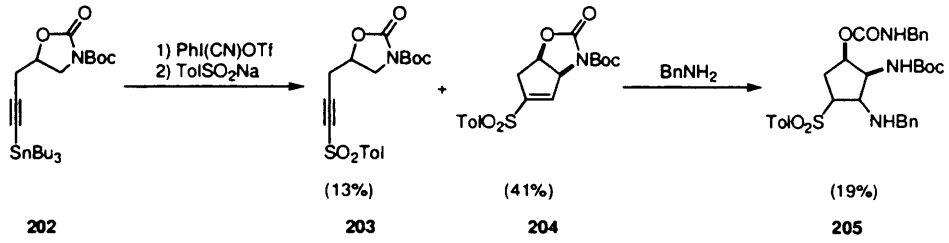
Scheme 31. Feldman's new plan towards (-)-agelastatin A

Preliminary studies were attempted on the racemic substrate **197** (Scheme 32). Thus, treatment of stannane **197** with Stang's reagent led to the alkynyl iodonium salt, and addition of this salt to a solution of sodium toluenesufinate afforded a mixture of the desired cyclopentene **199** along with the *O*-lone-pair insertion product **198**. Further elaboration of **199** into agelastatin A would require the stereoselective *N*-attachment of a pyrrole carboxamide unit at C(5a). This overall transformation was successfully accomplished by a preliminary conjugate addition of benzylamine to the convex face of the bicyclic olefin, and *N*-acylation of the resultant secondary amine with pyrrole-2-carboxylic acid chloride, which secured **200**. Unfortunately, attempted cleavage of the oxazolidinone unit in **200** failed, leading to the elimination product **201**.



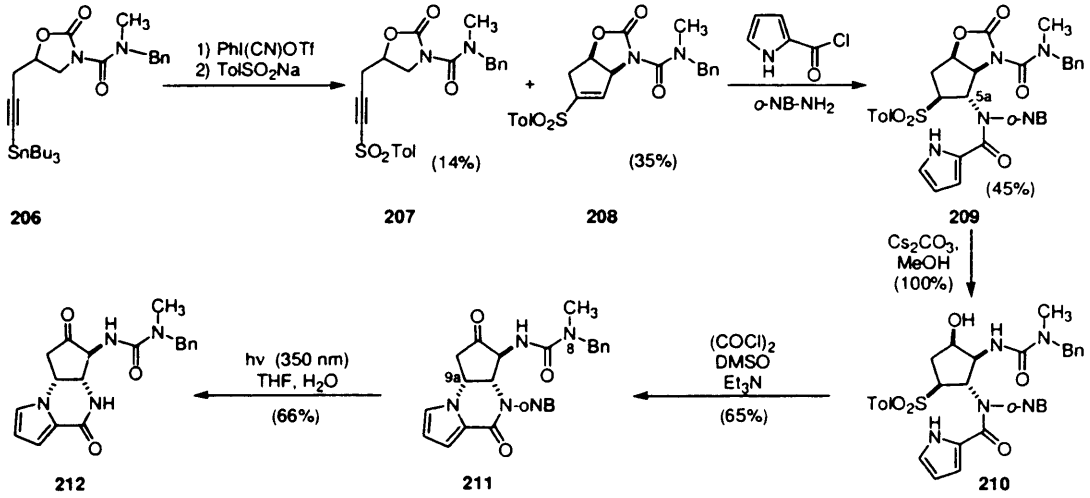
Scheme 32. Preliminary studies on the carbene insertion reaction outcome

In order to circumvent the difficulties associated with dihydrofuran formation, the alternative substrate **202** was investigated; it contained a Boc group instead of a Bn (Scheme 33). It was envisioned that the Boc group would serve a dual role in that it would enhance the lability of the oxazolidinone ring-system towards hydrolysis, and it would reduce the γ-oxygen lone-pair insertion by enhancing electron-withdrawal by the carbonyl group in the oxazolidinone system. Thus, the same iodination/cyclisation sequence performed on **202** afforded the desired cyclopentene **204** in 41% yield, and no *O*-lone-pair insertion product was detected. Instead, a 1,2-sulfone shift rearrangement product **203** was now co-produced in significant yield. Feldman explained this result by the fact that the hydrogen targeted for 1,5 CH-insertion was attached to a more electron deficient atom in **202** than in **197**, due to the presence of the electron withdrawing *N*-Boc group. This probably slows the rate of the carbene insertion, therefore increasing the occurrence of the sulfone rearrangement. Unfortunately however, this strategy ultimately had to be abandoned, after the attempted benzylamine conjugate addition to the carbon-carbon double-bond in **169** was complicated by concurrent attack of the amine to the carbonyl.



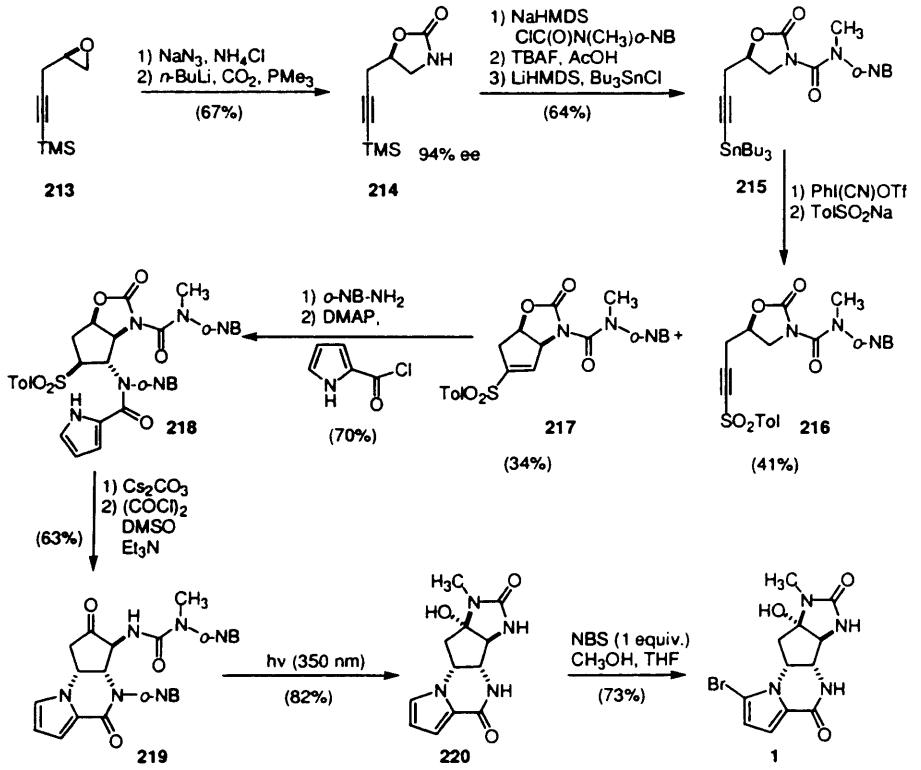
Scheme 33. The carbene insertion reaction on a revised substrate

Given these difficulties, it was eventually decided to investigate the effect of placing a less activating *N*-substituent on the oxazolidinone. A protected *N*-urea, such as *N*-$CON(CH_3)CH_2Ph$,[81] was considered, since it would lower the electrophilicity of the oxazolidinone carbonyl while setting the *N*-methyl urea encountered in the targeted natural product. As expected, the alkynyliodonium salt derived from **206** combined with sodium toluenesulfinate to yield the cyclopentene **208** along with the product of 1,2-sulfone shift **207**. The amounts of the two products were similar to those obtained with the *N*-Boc substrate **202**. Nucleophilic attack of *o*-nitrobenzylamine did not interfere with the oxazolidinone ring. The resulting secondary amine was acylated to furnish the C(5a) pyrrole carboxamide unit in **209**. Hydrolysis of the oxazolidinone ring proceeded quantitatively to give alcohol **210**. Exposure of this alcohol to Swern oxidation conditions initiated a sequence of reactions that included oxidation of the alcohol to the corresponding cyclopentanone, elimination of sulfinate to form a putative cyclopentenone, and finally internal conjugate addition of the pyrrole nitrogen onto the C(9a) position to form tricycle **211**. The *o*-nitrobenzyl group was efficiently removed by irradiation of **211**, to afford **212**. Remarkably, attempted hydrogenolysis of a *N*(5)-benzyl analogue of **211** led only to cleavage of the *N*(8)-benzyl group; hence, the ultimate choice of the *o*-nitrobenzyl group.



Scheme 34. Final modification of the *N*-protecting group

The asymmetric synthesis of (-)-agelastatin A (Scheme 35) started with the known alkynyloxirane **213**,[82] which was obtained from (*R*)-epichlorohydrin by a Jacobsen hydrolytic kinetic resolution.[83] Azide ring-opening, followed by reductive cyclization afforded oxazolidinone **214**. *N*-Acylation of **214** with *o*-NB-protected *N*-methyl carbamoyl chloride, followed by silicon-to-tin exchange at the alkyne terminus secured **215**. Exposure to Stang's reagent, and then to sodium toluene sulfinate procured the desired cyclopentene **217** in 34% yield, along with the rearrangement product **216**, now obtained in a much higher 41% yield. Conjugate addition of *o*-nitrobenzylamine proceeded nicely, and the resulting amine was acylated with pyrrole 2-carboxylic acid chloride as before, yielding **218**. Oxazolidinone hydrolysis, followed by Swern oxidation afforded **219**. Photochemical cleavage of the two *o*-NB groups procured (-)-debromoagelastatin A **220**. Selective bromination of the latter at C(1) could be efficiently achieved with less than 4% contamination by the dibromo analogue of **220**, using exactly 1 equivalent NBS in a solvent mixture of THF and MeOH.

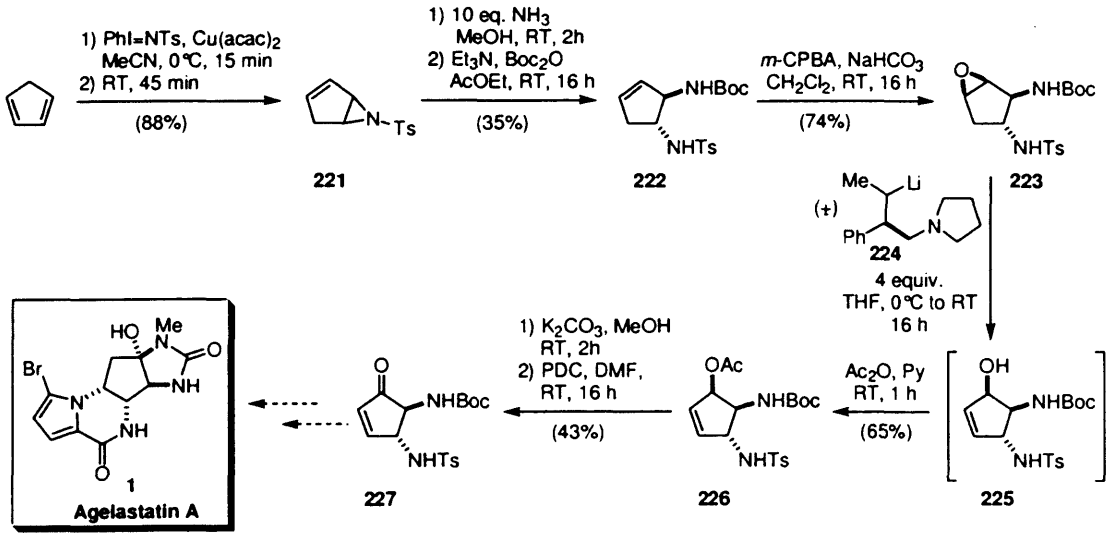


Scheme 35. Feldman's enantioselective total synthesis of (-)-agelastatin A

In conclusion, Feldman *et al.* completed an enantioselective total synthesis of (-)-agelastatin A starting from an enantiomerically enriched alkynyloxirane, obtained by Jacobsen hydrolytic kinetic resolution. The cyclopentane core of the natural product was fashioned by a carbene insertion reaction that employed an alkynyliodonium salt. A regioselective bromination of the debromo analogue of agelastatin A completed this total synthesis.

1.5.3. O'Brien's Approach to the Cyclopentane Core of Agelastatin A

During the course of their studies on cyclopentadiene aziridines, O'Brien and co-workers reported a concise racemic synthesis of the cyclopentenone **227** (Scheme 36), containing the *trans*-diamino functionality shown and appropriate stereochemistry for a possible future conversion to (±)-agelastatin A.[84] Thus, cyclopentadiene was directly converted to *N*-tosylaziridine **221** by reaction with PhI=NTs and 10 mol% of $Cu(acac)_2$, following a procedure reported earlier by Knight and Muldowney.[85] Regioselective ring-opening of *N*-tosylaziridine **221** with ammonia on the more activated allylic position, followed by protection of the resulting amine with a Boc group afforded cyclopentene **222** as the sole regioisomer of the reaction. Epoxidation of alkene **222** afforded epoxide **223** as a single diastereoisomer. In order to set the required distribution of hydroxyl (or keto) and diamino functionality present in agelastatin A, epoxide **223** was rearranged into the corresponding allylic alcohol by treatment with four equivalents of the racemic diamine-derived base **224** to give **225**. For isolation purposes, the crude alcohol was acetylated, securing **226**. Hydrolysis of the *O*-acetate and oxidation of the hydroxyl with PDC furnished cyclopentenone **227**, which could potentially be converted to racemic agelastatin A, as it contains the correct arrangement of *trans*-diamino functionality and the unsaturated enone present in the natural product. It should also be possible to run the lithium amide-mediated rearrangement of epoxide **223** under kinetic resolution conditions, in order to generate allylic alcohol **225** in an enantiomerically enriched form, although this was not attempted in this particular study.

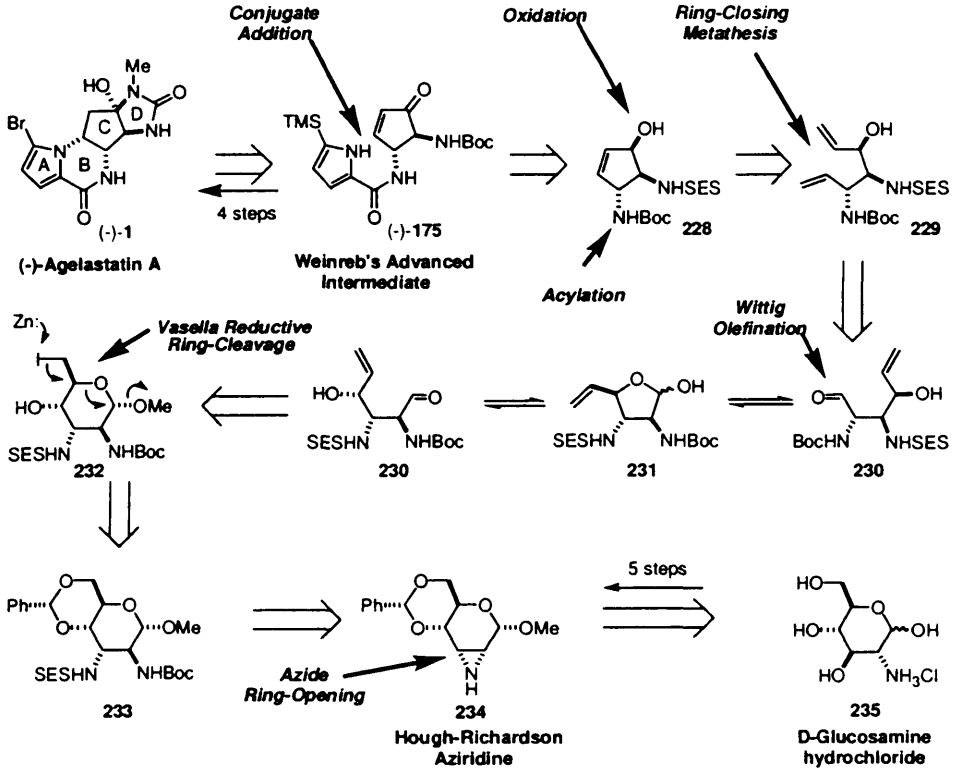


Scheme 36. O'Brien's approach to the cyclopentane core of (±)-agelastatin A

Chapter 2: First Generation Strategy for (-)-Agelastatin A

2.1. Retrosynthetic Analysis of (-)-Agelastatin A

In their racemic route to agelastatin A, Weinreb and co-workers successfully converted enone **175** into the natural product by a four-step sequence that involved a Michael-type addition for construction of the ABC core.[68] Given that our primary interest in synthesising (-)-agelastatin A was to obtain sufficient quantities of the natural product to do more comprehensive biological testing, and also put in place a route for obtaining analogues, it seemed logical to capitalize on Weinreb's past successes in this area, in our planning of an enantiospecific pathway to agelastatin A. Accordingly, we decided to intersect with the known enone **175**, except now, this would be prepared in optically pure form.



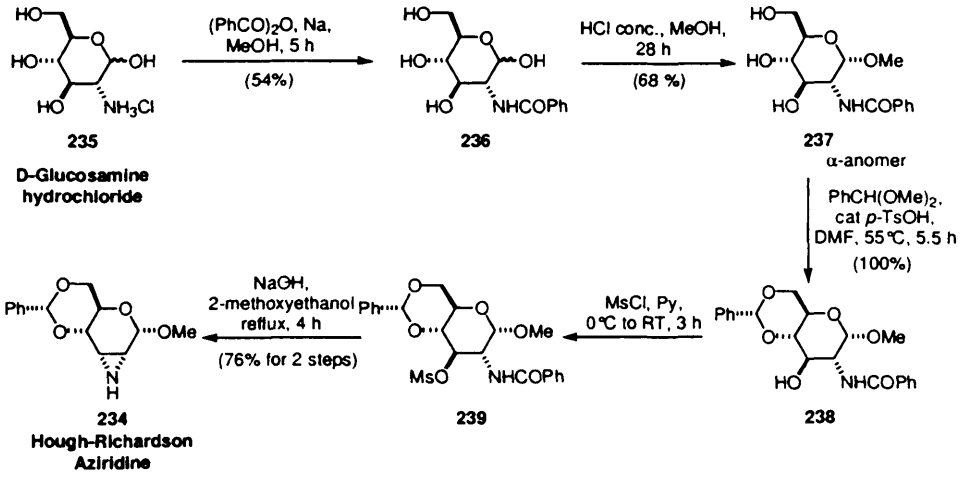
Scheme 37. Initial retrosynthetic plan for agelastatin A

Enone (-)-**175** appeared derivable from **228** by oxidation of the allylic alcohol function and acylation of the *N*-Boc protected amine. A ring-closing metathesis reaction would be employed for cyclopentene ring-assembly in **228**. Diene **229** would itself be prepared from the corresponding aldehyde **195** by a Wittig-type olefination. The fact that this aldehyde would

probably exist as an equilibrating mixture of hemiacetal anomers was not a major concern at this stage, since this sort of compound is known to undergo facile Wittig reaction, provided that the hemiacetal is deprotonated prior to olefination.[86] We intended to use a Vasella reductive ring cleavage[87] to prepare the aldehyde **230** from iodopyranoside **232**, and the latter would be obtained from the corresponding benzylidene acetal **233**. A regioselective *trans*-diaxial ring-opening with azide ion was envisaged for setting up the vicinal diamido functionality present in **233**. Such a sequence would involve the known Hough-Richardson aziridine **234**, which is available in 5 steps from D-glucosamine hydrochloride **235**.

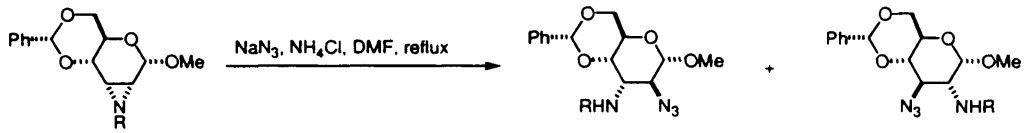
2.2. Attempted Implementation of the First-Generation Synthetic Strategy for (-)-Agelastatin A

An early objective in our route to (-)-agelastatin A was the synthesis of aziridine **234** from D-glucosamine hydrochloride. This could efficiently be performed following the reported procedure of Hough and Richardson (Scheme 38).[88] Their procedure commenced with the chemoselective *N*-acylation of cheap and readily available D-glucosamine hydrochloride **235** with benzoic anhydride in methanolic sodium methoxide to obtain **236**;[89] it continued with a Fischer glycosidation to form α-methylpyranoside **237**. *O*-Benzylidenation of **237** was most conveniently achieved using benzaldehyde dimethylacetal in DMF using a catalytic amount of *p*-toluenesulfonic acid at 55°C. Compound **238** was then *O*-mesylated at C(3) using methanesulfonyl chloride in pyridine. Upon treatment of **239** with sodium hydroxide in 2-methoxyethanol, it underwent ring closure to form the aziridine ring with concomitant loss of the labile *N*-benzoyl unit, securing **234**.[90] It should be noted that all the compounds in this sequence are highly crystalline, and all the purifications can readily be effected on large scale by crystallisation. As a consequence, aziridine **234** could be prepared on 0.5 kg scale.



Scheme 38. Preparation of aziridine **234** following the route of Hough and Richardson

During their work on epimino derivatives of glycosides, Guthrie and Murphy observed that the ring-opening of variously protected aziridines by nucleophilic species such as azide ion proceeded by a regioselective *trans*-diaxial pathway (Scheme 39). Thus, treatment of aziridines **234** and **240** with 4 equivalents of sodium azide in boiling DMF in the presence of ammonium chloride, to quench the amide anion as it formed, afforded the altropyranoside **243** exclusively. In the case of *N*-acetylaziridine **240**, the acetyl group was probably cleaved off by hydrolysis prior to ring-opening of the parent epimine, since only amine **208** was isolated from the reaction mixture. When a more stable *p*-toluenesulfonyl protecting group was used as in **241**, the corresponding altropyranoside **245** was obtained. Surprisingly, the same conditions applied to *N*-benzoylaziridine **242** were claimed to give the glucopyranoside **246b** *exclusively* in 70% yield. However, a subsequent reinvestigation by Chaby and coworkers in 1998 showed that the major component of this reaction mixture was indeed the *trans*-diaxial ring opening product **246a**, which was formed in 70% yield alongside a 25% yield of the highly crystalline D-glucopyranoside **246b**.[91] In all cases, the protected aziridines reacted much faster than their parent aziridines.



234, R = H
240, R = Ac
241, R = *p*-Ts
242, R = Bz

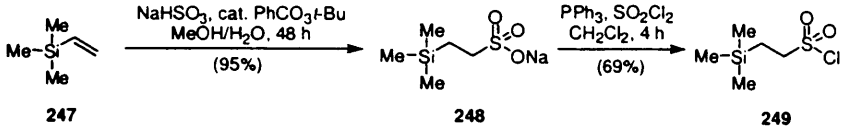
243, R = H (82%)
244, R = H (65%)
245, R = *p*-TsOH (41%)
246a, R = Bz (70%)

246b, R = Bz (25%)

Scheme 39. Ring-opening of differently-protected aziridine with sodium azide

Given its great stability to the various conditions that would be used in our planned synthesis of (-)-agelastatin A, a sulfonyl group seemed like a logical choice for attachment to the aziridine ring of **234**. Nevertheless, removal of this group can often require harsh conditions, especially on primary amines. In light of this, the SES (β-trimethylsilylethanesulfonyl) protecting group seemed like an attractive choice. This group, designed by Weinreb for the protection of primary and secondary amines, combines the stability of sulfonamides with the lability of β-silylethyl species.[69] *N*-SES protected sulfonamides are stable to Brönsted and Lewis acids (refluxing TFA, 6M HCl in refluxing THF, BF_3 etherate, $LiBF_4$ in refluxing MeCN); however, they are claimed to be easily cleaved, in excellent yield, with caesium fluoride (2-3 equiv.) in DMF

after several hours exposure, or with TBAF.$3H_2O$ (3 equiv.) in refluxing MeCN. Note that *N*-SES pyrrole can be cleaved with 1M TBAF in THF at room temperature.

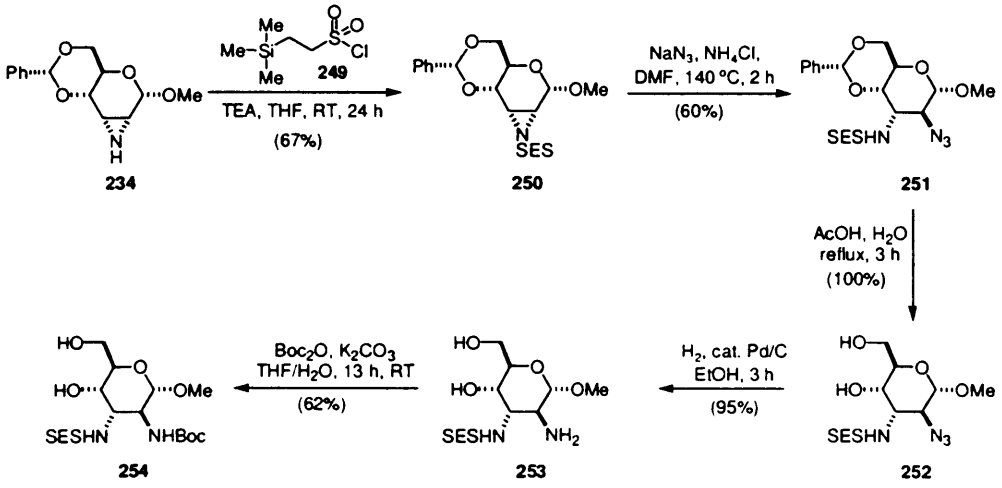


Scheme 40. Optimal preparation of SES chloride

The preparation of SES chloride (Scheme 40) proceeds by a radical addition of sodium bisulfite onto the carbon-carbon double bond of vinyltrimethylsilane **247**, to afford toluenesulfonate salt **248**. Conversion of this sulfonate to the corresponding sulfonyl chloride, using PCl_5 in carbon tetrachloride afforded a 1.5:1 mixture of the sulfonyl chloride and the corresponding anhydride, respectively. The modified procedure reported by Weinreb *et al.*,[70] which employs thionyl chloride and a catalytic amount of DMF, afforded exclusively the corresponding sulfonic acid on large scale. An alternative procedure by Huang and Widlanksi was used instead, and adapted for the large scale preparation of SES chloride.[92] Thus, sodium sulfonate **248** was treated with triphenylphosphine and sulfuryl chloride in dichloromethane to give SES chloride **249** in 69% yield on large scale (typically 100 g). An improved method for preparing SESCl has recently been reported by Robins *et al.*.[93] Their method also utilises thionyl chloride as the chlorinating agent, but a stoichiometric amount of DMF is used, affording SESCl free from anhydride or acid.

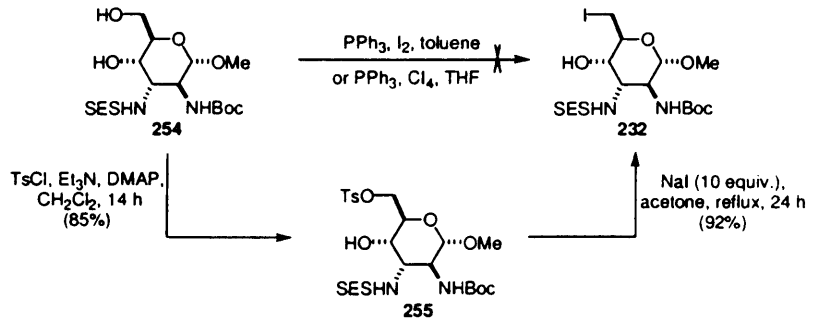
Thus, protection of aziridine **234** was achieved with 1.2 equiv SES chloride and excess triethylamine in THF. The reaction proceeded nicely to give the *N*-SES protected aziridine **250** in 67% yield (Scheme 41). Ring-opening of this compound with sodium azide, according to the protocol of Guthrie and Murphy, afforded altropyranoside **251** as the sole regioisomer in 60% yield. Infra-red analysis of this compound showed the expected N_3 stretching band at 2105 cm^{-1}. The *trans*-diaxial relationship between the C(2) and C(3) substituents in **251** was confirmed by the 500 MHz ^{1}H-NMR spectrum of **251** in $CDCl_3$, which showed a small coupling constant (J = 2.7 Hz) between H(2) and H(3), indicating a *trans*-diequatorial relationship between these protons. Next, the benzylidene acetal was cleaved off by heating **251** in a 4:1 mixture of acetic acid/water. Catalytic reduction of the azido group in **252** was conveniently effected by hydrogenation over a 10% wet palladium on carbon catalyst in ethanol. Subsequent protection of the primary amine with Boc_2O was regioselectively achieved using Carpino's biphasic conditions,[94] producing **254** in 62% yield. Success in this reaction was evidenced by infra-red analysis of the product, which showed disappearance of the N_3 stretching band at 2105 cm^{-1},

and by 500 MHz ^{1}H-NMR spectrum of **254** in $CDCl_3$, which showed the presence of an amide-NH at 5.18 ppm and two hydroxy-protons at 3.06 and 2.52 ppm.



Scheme 41. Installation of the diamido functionality within the pyranoside ring system

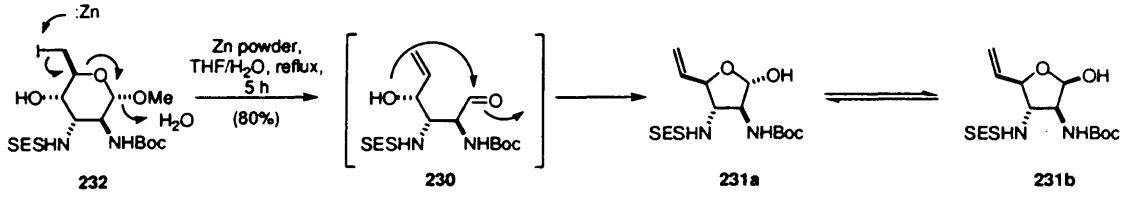
In order to access the key iodide **232** needed for the Vasella reductive ring-cleavage, the selective iodination of primary alcohol **254** was next investigated. Regioselective halogenation of the C(6) position of monosaccharide glycosides is well documented in the literature. The combination of triphenylphosphine and *N*-halosuccinimide[95] or carbon tetrahalide[96] are convenient methods for the direct substitution of primary alcohol by a halide (Cl, Br, I) in the presence of one or more secondary hydroxyl groups. Another convenient method using triphenylphosphine, iodine and imidazole has also been reported by Samuelsson.[97] Unfortunately, none of these methods were effective for converting diol **254** into iodopyranoside **232**, the starting material usually remaining untouched even after prolonged reaction times (24 hours). In light of these failures a two-step procedure was used instead (Scheme 42).



Scheme 42. Iodination of diol **254**

Thus, regioselective tosylation of the primary hydroxyl in **254** with *p*-toluenesulfonyl chloride and triethylamine in dichloromethane at 0°C afforded tosylate **255** in 85% yield. Evidence for the selective *O*-tosylation of the primary hydroxy group was provided by the 500 MHz ^{1}H-NMR spectrum of **255** in $CDCl_3$, which showed a downfield shift of H(6) from 4.11 and 3.90 ppm to 4.36 and 4.21 respectively. Subsequent nucleophilic displacement with 10 equiv. sodium iodide in refluxing acetone produced **232** in 92% yield. Evidence for incorporation of the iodo substituent into **232** was provided by its 125 MHz ^{13}C-NMR spectrum in $CDCl_3$, which showed C(6) at the very high field position of 6.6 ppm.

With iodopyranoside in hand, its reductive ring-cleavage was attempted with a view to securing **229** (Scheme 43). Ever since Bernet and Vasella first described the zinc-promoted ring-fragmentation of 6-halo derivatives of α-pyranosides, this methodology has been widely used as an entry to highly functionalised chiral δ,ε-unsaturated aldehydes starting from carbohydrates. It proceeds by a preliminary oxidative addition of the Zn into the C-X bond, followed by a β-elimination that produces methanol. Treatment of iodide **232** with zinc dust (size <10 μm) in a refluxing mixture of THF/water (4:1) afforded a single product, as evidenced by TLC. Infra-red analysis of this compound did not show the expected strong stretching band of aldehydes at 1720 cm^{-1}. 500 MHz ^{1}H-NMR analysis of this compound in $CDCl_3$ revealed that it consisted of a 1:1 mixture of the two anomeric hemiacetals **231a** and **231b**.

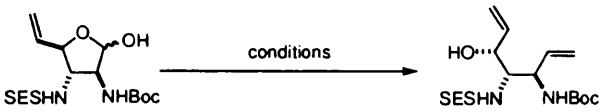


Scheme 43. The Vasella reductive ring-cleavage

The next step in our strategy was the olefination of hemiacetal **231** to form the corresponding diene **229**. Standard Wittig olefination conditions using methyl triphenylphosphoranylidene, prepared *in situ* from methyl triphenylphosphonium bromide and *n*-BuLi in THF (entry 1, Table 2), or methyl triphenylphosphonium bromide and *tert*-BuOK in THF (entry 2, Table 2), left the starting material untouched. Next, a Tebbe olefination reaction was attempted (entry 3).[98] The Tebbe reagent was prepared *in situ* from a commercial solution of the precursor by addition of a catalytic amount of sodium hydroxide. A complex mixture of compounds was formed, from which none of the desired olefin could be isolated. The recently

reported Takai olefination[99] was next investigated (entry 4), since this method has proved useful in a number of related substrates. Unfortunately, all attempts at converting hemiacetal **231** into **229** remained unsuccessful.

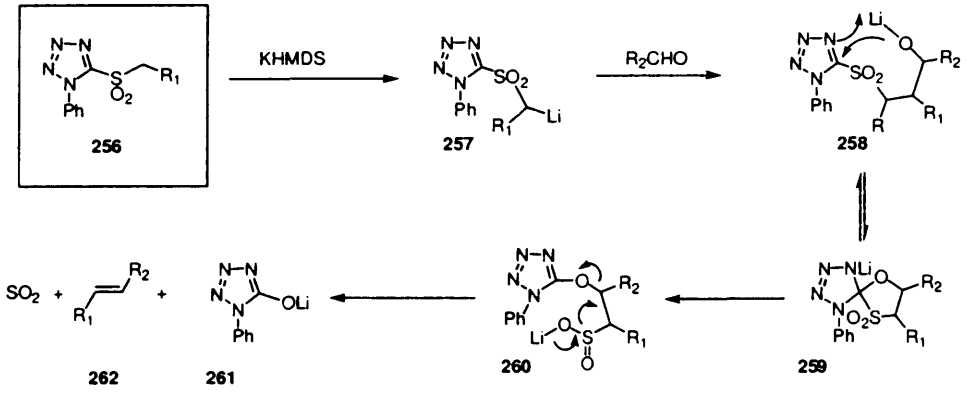
Table 2. Attempts at olefinating the hemiacetal



231 **229**

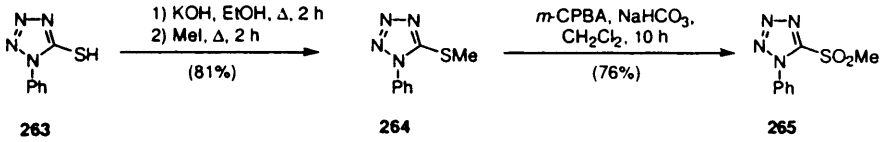
Entry	Conditions	Yield
1	*n*-BuLi (5 eq.), $[Ph_3PCH_3]Br$ (5 eq.), THF, RT to reflux	no reaction
2	*t*-BuOK (3.2 eq.), $[Ph_3PCH_3]Br$ (2.2 eq.), THF, RT to reflux	no reaction
3	$Cp_2TiCH_2AlCl(CH_3)_2$ (1eq.), THF/PhMe, 0 °C to RT	mixture
4	Zn (10 eq.), CH_2I_2 (3 equiv.), TMSCl (3 eq.), cat. $PbCl_2$ (0.1 eq.), THF, RT	no reaction

The new olefination method recently reported by Kocieński and co-workers[100] was also investigated. The Kocieński method involves the use of a lithiated *N*-phenyltetrazole sulfone of general structure **257** which adds to carbonyls in the manner shown below (Scheme 44). This sulfone gives significantly higher yields than the benzothiazolic counterparts previously reported by Julia,[101] possibly because the phenyltetrazolyl anion is less prone to dimerisation. The Kocieński methodology was successfully applied to a synthesis of herboxidene by his group.[102] Nevertheless, no previous reports were found for the use of these reagents on hemiacetals.



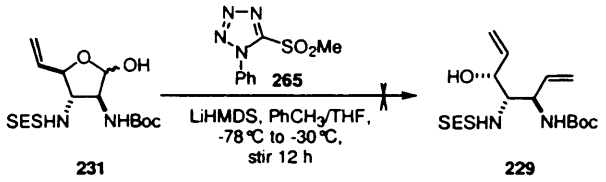
Scheme 44. Mechanism of Kocieński's new olefination method

For the olefination of hemiacetal **231**, the new sulfone **265** was prepared by the route of Kocieński.[102] Thus commercially available 1*H*-phenyltetrazol-5-thiol **263** was alkylated with iodomethane after deprotonation with potassium hydroxide, and the resulting thioether **264** was oxidised with *m*-chloroperoxybenzoic acid to give sulfone **265**.



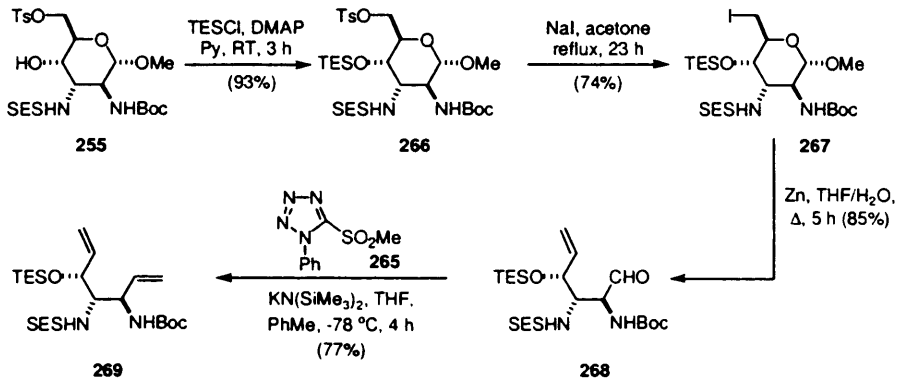
Scheme 45. Preparation of 5-methanesulfonyl-1-phenyl-1*H*-tetrazole

Unfortunately, the slow addition of LiHMDS to a mixture of hemiacetal **231** and sulfone **265** in THF at –78°C, followed by warming of the reaction to mixture to –30°C left **196** intact after 12 hours (Scheme 46).



Scheme 46. Atempted olefination of hemiacetal **231** with sulfone **265**

Since all our attempts to olefinate **231** were unsuccessful, it seemed necessary to protect the secondary alcohol of **232** in order to prevent the formation of this hemiacetal. The TES protecting group was selected, given its acceptable stability to base and its ease of deprotection with fluoride ion or mild acids.[103] Thus a step backward was taken in the route to (-)-agelastatin A, and alcohol **255** was treated with chlorotriethylsilane and DMAP in pyridine to afford the fully protected pyranoside **266** (Scheme 47). Nucleophilic displacement with iodide as before produced iodopyranoside **267**. The Vasella reductive ring-cleavage afforded aldehyde **268** in 85% yield, as evidenced by the presence of a singlet at δ 9.60 ppm in the 500 MHz proton-NMR spectrum of the isolated product in $CDCl_3$. However, repeated efforts to olefinate aldehyde **268** using the Wittig and Tebbe reaction failed, the starting aldehyde always being left intact. Fortunately, when aldehyde **268** was treated with sulfone **265** and potassium hexamethyldisilazide, diene **234** was obtained in 77% yield. Remarkably, when lithium hexamethyldisilazide was used as the base, no reaction occurred. Evidence for the formation of **269** was given by 500 MHz ^{1}H-NMR analysis in $CDCl_3$, which contained resonances for 3 olefinic protons at δ 5.77, 5.25, and 5.22 ppm.



Scheme 47. Preparation of the diene

With diene **269** in hand, we next addressed the key ring-closing metathesis (RCM) reaction[104] on **269** to form the corresponding cyclopentene. Amongst the most active ring-closing metathesis catalysts available, the Schrock molybdenum alkylidene **271** and the Grubbs-Hoveyda catalyst **276** are now commercially available. The Schrock catalyst is hardly affected by the electronic properties of the olefinic substrates and reacts with both electron-rich olefins (enol ethers) and electron-deficient olefins (acrylates). For a long time, it was the only catalyst to allow the formation of tri- and even tetrasubstituted olefins by RCM. Unfortunately however, this complex is extremely sensitive towards oxygen and moisture, and must be handled using Schlenk techniques. Moreover, the "hard" Mo^{VI} center is often deactivated by "hard" nucleophiles such as nitrogen substituents on the olefin that form unreactive chelates. For these reasons, we ruled out use of the Schrock catalyst to mediate the conversion of **269** into **270**.

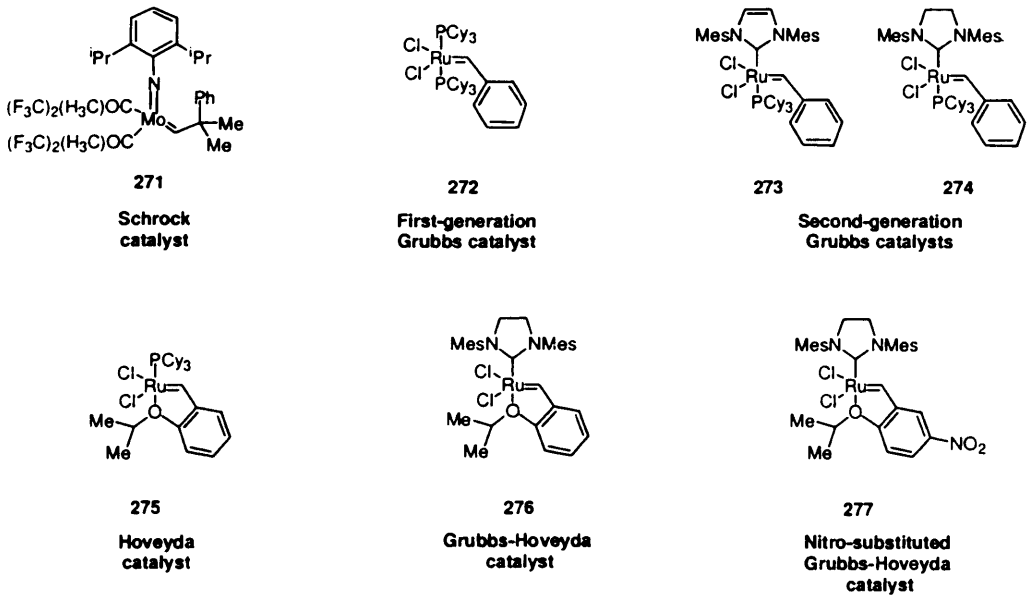
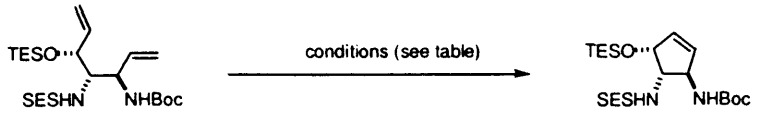


Figure 7. RCM catalysts

The ruthenium-based first-generation Grubbs catalyst **272**[105] was a much more attractive catalyst for the synthesis at hand given its high activity for all types of alkene metathesis reactions, its spectacular tolerance of a wide array of functional groups, and its reasonable stability towards oxygen, water and minor impurities in the solvents. Generally speaking, its ease of handling and commercial availability makes it an exceedingly practical catalyst for use in large scale syntheses. It is also commercially available. However, this catalyst often fails to react with electron-deficient olefins, such as π-conjugated olefins (enones, enoic esters). Given that **269** contained non-conjugated and reasonably electron-rich alkenes, we anticipated success in the RCM reaction with **272**. Unfortunately, catalyst **272** showed no reactivity towards **269** when it was heated at reflux in methylene chloride. Possibly, this lack of reactivity was due to deactivation of the catalyst by its coordination with the NH-substituents on the substrate.

Table 3. Ring-closing metathesis reaction of diene **269**



269 **270**

Entry	Catalyst (mol%)	Solvent	Time	Yield
1	**272** (10%)	CH_2Cl_2	8 h	0 %
2	**272** (5%)	PhMe	28 h	0%
3	**274** (6%)	PhMe	8 h	53%
4	**276** (5%)	PhMe	15.5 h	92 %

Detailed mechanistic studies have shown that the dominant pathway for productive metathesis involves the dissociation of one of the two PCy_3 ligands from **272**. The replacement of one of the phosphine units by a more Lewis basic and sterically demanding ligand, such as the *N,N'*-disubstitued 2,3-dihydro-1*H*-imidazol-2-ylidene unit led to the second-generation catalyst **273**.[106] The combination of a kinetically inert *N*-heterocyclic carbene with a coordinatively labile phosphine somewhat limits the dissociative pathway. This probably explains the greater stability of catalyst **273** towards air/water, and its enhanced reactivity towards electron-deficient olefins. Further improvement was achieved by using the saturated analogue of 2,3-dihydro-1*H*-imidazol-2-ylidene, as in catalyst **274**[107] The lack of carbene stabilisation provided by the absence of a π-donating effect renders the carbene more basic than its unsaturated analogue. This leads to a catalyst with greater reactivity and better

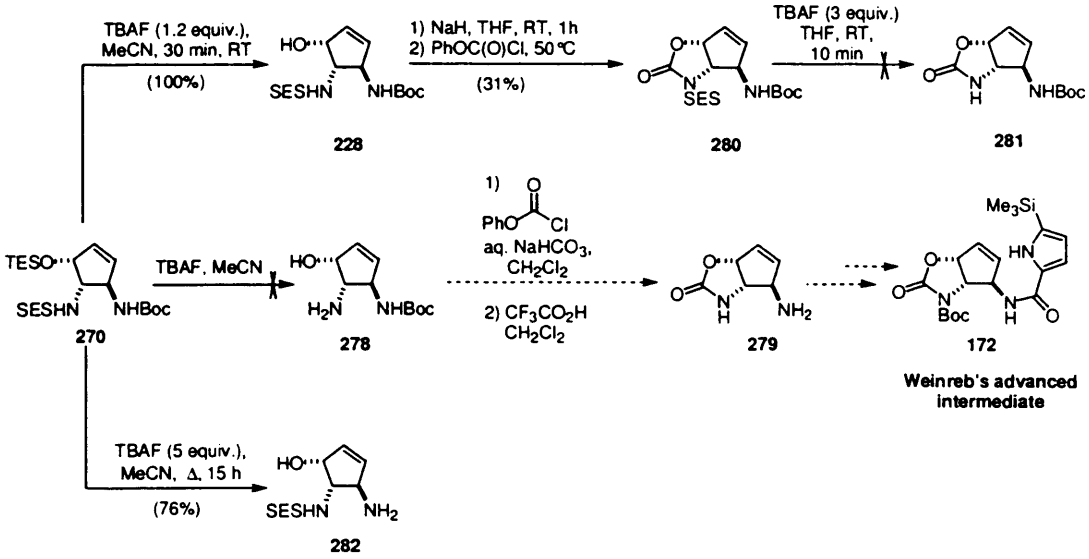
compatibilty towards functional groups (*i.e.* allylic alcohols). Reaction of diene **279** with **274** did afford some of the product **270** in refluxing toluene, but the reaction seemed to stop after *ca.* 50% conversion. Nevertheless, this promising result raised our hopes and prompted us to examine the more active Grubbs-Hoveyda catalyst **276**.

Detailed studies of **276** by Hoveyda have shown that the Lewis basic isopropoxy group stabilises the complex in its resting state, and that it readily opens a coordination site in the presence of the substrate. Moreover, increased steric hindrance around the Ru-centre protects the complex from side-reactions, such as carbene oxidation. Recently, the nitro-substituted Grubbs-Hoveyda catalyst **277** has been reported by Grela and co-workers.[108] The presence of a nitro group on the benzylidene ring is thought to decrease the electron density at the oxygen atom. This leads to an increased initiation rate and therefore an increased catalytic activity. Fortunately, the Grubbs-Hoveyda catalyst **276**[109] became commercially during the course of the present study. To our great delight, treatment of diene **269** with 5 mol% of the Grubbs-Hoveyda catalyst in toluene at reflux afforded the cyclopentene **270** in an excellent 92% yield after 12 h. The reaction was performed using non-distilled solvent in a reaction vessel open to the air.

The successful preparation of cyclopentene **270** now potentially allowed us to channel into the final stages of the Weinreb route. We originally envisioned that the two silyl protecting groups of **270** would be easily removed with a fluoride source to afford **278**, which would subsequently be converted into the amine **279** by formation of the oxazolidinone with phenyl chloroformate and deprotection of the Boc group with TFA. Acylation of **279** and protection of the oxazolidinone nitrogen atom with a Boc would then provide Weinreb's advanced intermediate **172**. Unfortunately, our attempts to remove the SES group from **270** with various fluoride sources (CsF, DMF, 95°C or TBAF, THF, 50°C)[69] were unsuccessful. On one occasion, a single product was isolated from the reaction of **270** with 5 equiv. of TBAF in acetonitrile at 80°C; its structure was shown to be that of **282** based on mass spectrometry and ^{1}H-NMR analysis. It is likely that the residual water present in the commercial 1M TBAF solution causes cleavage of the Boc group. Why the SES group should have remained intact is unclear.

A closer examination of the literature showed that the Ward group had experienced similar problems when attempting to remove the SES group from primary amines with TBAF in THF at reflux or with CsF in DMF at 95°C, during the course of their studies on actinobolin and bactobolin.[110] Whether TBAF solutions (anhydrous or with 5% water) or CsF were used, all methods failed to produce the desired product. A recent report by Campbell and Hart indicated that the SES group could be removed from *N*-acyl SES sulfonamides under mild conditions.[111] Therefore, we decided to prepare oxazolidinone **280** and attempt the removal of the SES group on this substrate, as this structure would get us closer to Weinreb's intermediate **172** while enhancing the lability of the SES group. Thus, sulfonamide **271** was treated with sodium

hydride, followed by phenyl chloroformate to form **280** in an unoptimised 31% yield. Unfortunately, treatment of this compound with TBAF in THF did not afford the desired unprotected oxazolidinone **281**, but rather, some presently unidentified product.

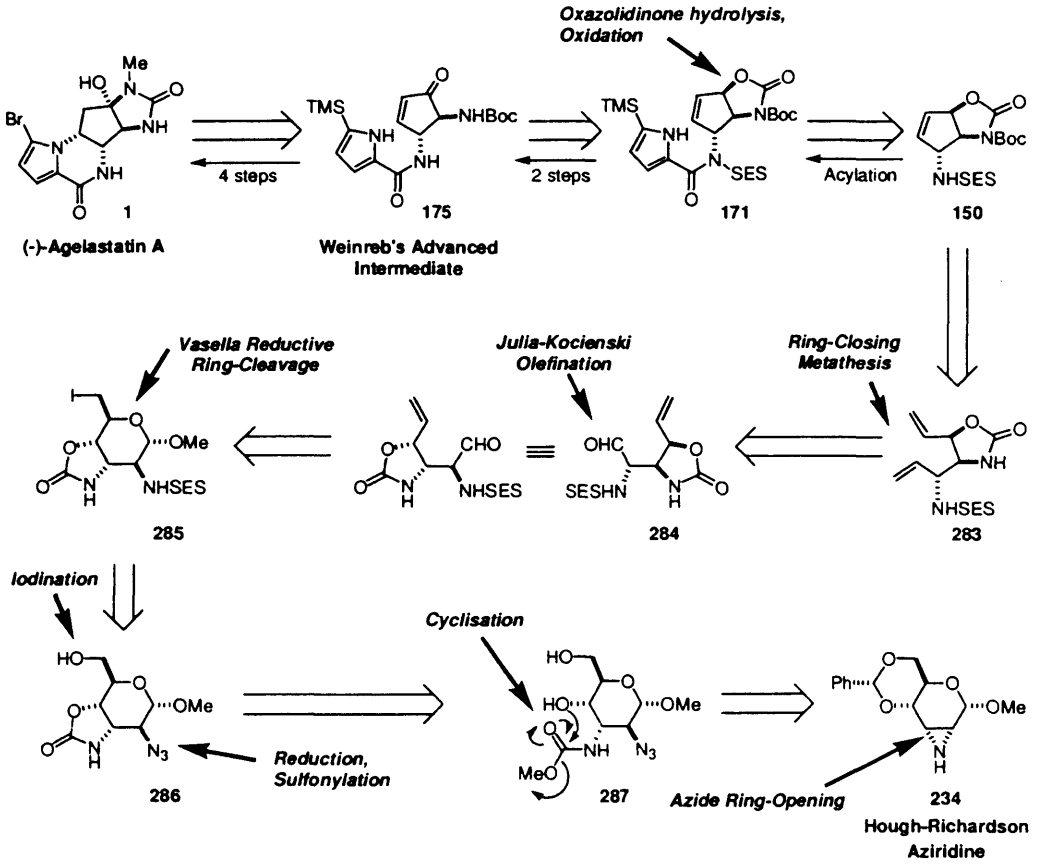


Scheme 48. Attempted preparation of Weinreb's intermediate

Chapter 3: Second Generation Strategy to (-)-Agelastatin A

3.1. Revised Retrosynthetic Plan

Given the problems that we had encountered in the deprotection of the SES group, we now decided to re-evaluate our strategy (Scheme 49). We resolved to comply with Weinreb's arrangement of protecting groups, and attempted the preparation of oxazolidinone **171**. Previously, this compound had been converted into the advanced intermediate **175** in two steps, by oxazolidinone hydrolysis and oxidation of the resulting alcohol. Pyrroloamide **175** itself was previously obtained by Weinreb from sulfonamide **150** by acylation with the pyrrole-2-carboxylic acid chloride derivative **170**. Returning to our own retrosynthetic analysis, **150** appeared derivable from the corresponding diene **283** by a Grubbs-Hoveyda ring-closing metathesis reaction. The Julia-Kocieński method would again be used to prepare **283** from aldehyde **284**, which would already bear the oxazolidinone functionality present in intermediate **171**.

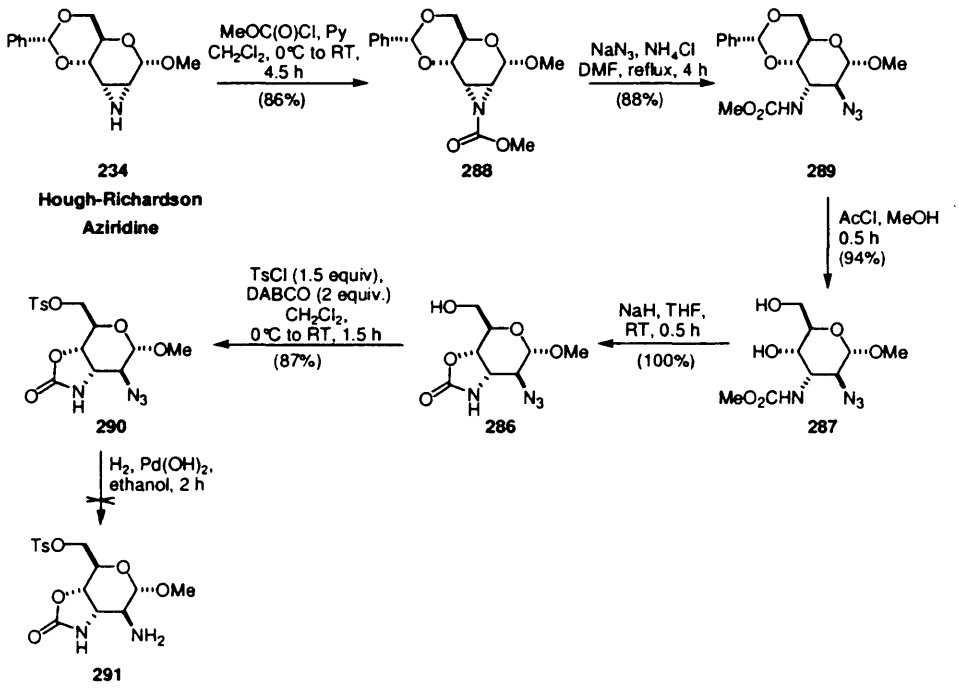


Scheme 49. Revised retrosynthetic plan

As before, a Vasella ring-cleavage would be used to access aldehyde **284** from iodide **285**; the latter would itself be obtained from the azido-alcohol **286** by reduction, acylation, and iodination of the alcohol functionality. The oxazolidinone ring would be assembled from diol **287** by intramolecular cyclisation of the secondary alcohol onto the adjacent *cis* methyl carbamate function. Finally, carbamate **287** would be prepared by azide ring-opening of a conveniently activated derivative of the Hough-Richardson aziridine **234**.

3.2. Attempted Implementation of the New Route

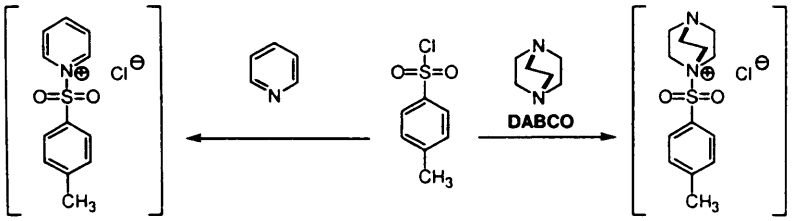
The new methoxycarbonyl protecting group on the aziridine ring would serve the dual role of activating the regioselective diaxial ring-opening as well as providing the carbonyl group of the oxazolidinone ring system. Thus, the Hough-Richardson aziridine was treated with methyl chloroformate to afford the carbamate **288** in 86% yield (Scheme 50). Although azide ring-opening of carbamate derivatives of **199** has not been reported, we were pleased to find that treatment of **252** with 4 equiv. sodium azide in DMF at reflux afforded exclusively the D-altropyranoside **289** in excellent yield. Removal of the benzylidene acetal from **289** was conveniently achieved by treating **289** with HCl in methanol. This was conveniently formed *in situ* by addition of acetyl chloride to anhydrous methanol at 0°C. Compound **287** was obtained in 94% yield.



Scheme 50. Implementation of the new route

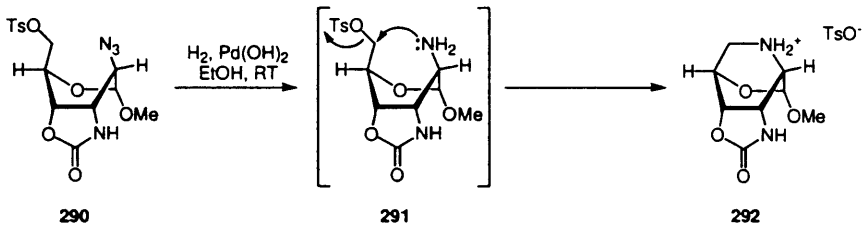
When the resulting diol was exposed to 1.5 equiv. sodium hydride in THF, the oxazolidinone **286** was formed in quantitative yield. The reaction was conducted at low

concentration (8×10^{-5} M) to favour the intramolecular process. Reasoning that reduction of the azido group at this stage would expose three nucleophilic functionalities that would be difficult to manage, we delayed this reduction step and attempted selective tosylation of the primary alcohol, in the presence of the very nucleophilic nitrogen of the oxazolidinone. We hoped that the less hindered alcohol in **286** would tosylate preferentially to this nitrogen. In this regard, the standard tosylation procedure (TsCl 1.1 equiv., triethylamine, DMAP, CH_2Cl_2) afforded a 1:1 mixture of the mono-*O*-tosylated and *N,O*-ditosylated oxazolidinones. Given that pyridine is known to catalyse this transformation by formation of an activated pyridinium tosylate salt (Scheme 51), we hypothesised that the salt generated from DABCO might preferentially react with the primary OH.[112] Indeed, treatment of **286** with 1.5 equiv. of *p*-TsCl and 2 equiv. of DABCO in CH_2Cl_2 produced *O*-tosylated alcohol **290** in an excellent 87% yield, without any ditosylation product being detected by TLC. Confirmation that the sulfonylation occurred at the primary OH was given by 500 MHz ^{1}H-NMR analysis of **290** in $CDCl_3$, which showed the deshielded oxazolidinone NH at 6.12 ppm, and the downfield chemical shift of the two C(6)-H at 4.25 and 4.17 ppm.



Scheme 51. Formation of activated tosylation agents with DABCO and pyridine

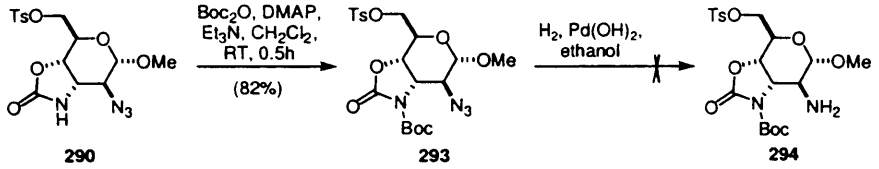
With *O*-tosylate **290** in hand, reductive hydrogenation of the azido grouping was attempted by stirring **290** under a saturated hydrogen atmosphere with 20% palladium hydroxide on carbon in ethanol. Although complete disappearance of the starting material was observed by TLC after 2 hours, no product could be isolated from the reaction mixture. Careful observation of the three-dimensional structure of **290** showed that the presence of the fused oxazolidinone ring greatly facilitates attainment of a boat conformation in the pyranoside ring. As a consequence, the transient nucleophilic amino group of **291** would be in a favourable position to effect an internal nucleophilic displacement of the tosylate, to afford **292**, which would probably stick to the metal catalyst. Alternatively, polymerisation may also have occurred. Given our inability to isolate any product from this reduction, it is not possible at the present moment to positively say what actually happened.



290 291 292

Scheme 52. Putative intramolecular cyclisation of amine **291**

Reasoning that the presence of a Boc group on the oxazolidinone would probably destabilise the boat-like conformation of **290**, and help prevent the undesired intramolecular cyclisation, we set about preparing **293** from the oxazolidinone **290**. When **293** was submitted to the catalytic hydrogenation protocol, again, no product could be isolated from the reaction mixture, and the starting material was found to completely disappear after 2 h according to TLC analysis.



290 293 294

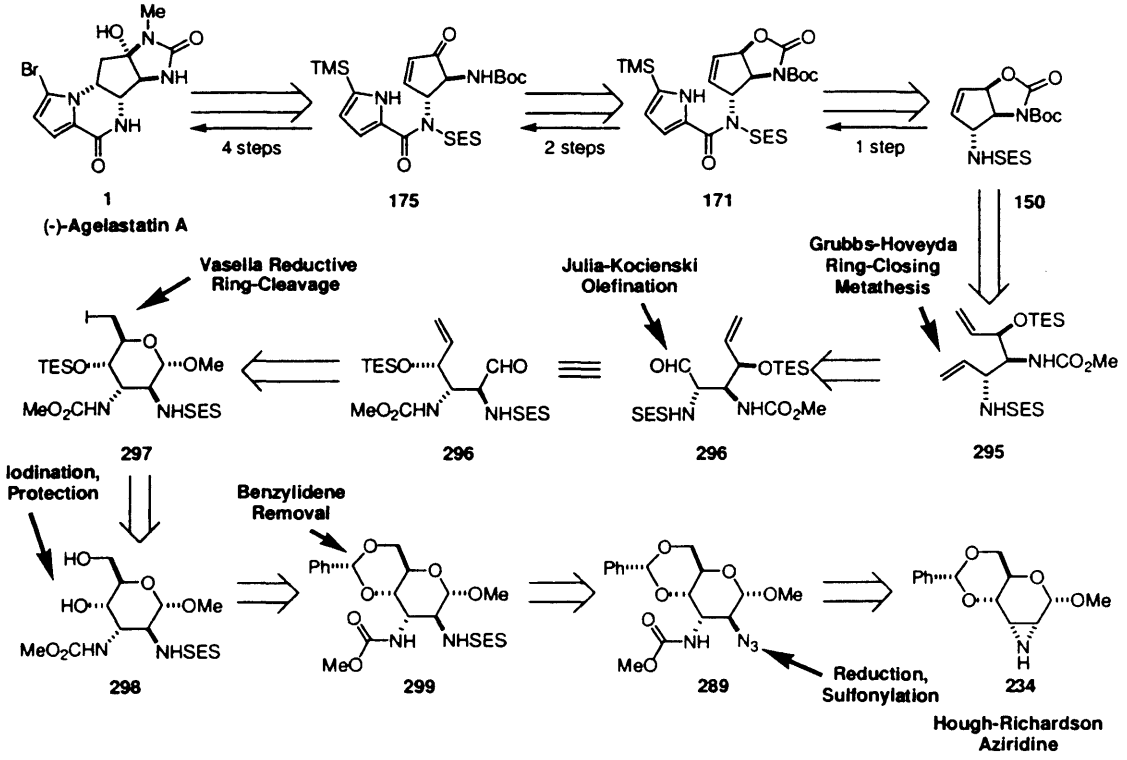
Scheme 53. Preparation of Boc-protected oxazolidinone **293** and attempted hydrogenation

In conclusion, incorporation of the oxazolidinone ring at an early stage of the route seemed to create problems since it changed the three-dimensional structure of the glycoside skeleton, and it appeared to modify the reactivity of the functionalities attached to it. Not only was the reduction of the azide problematical when a leaving group was attached at C(6), but we now foresaw that the Vasella ring-cleavage would be potentially troublesome since the favourable *trans*-diaxial relationship between the C(1)-OMe and the C(6)-CH_2X bonds would no longer be present. Therefore, we considered it necessary to slightly change the planned route and delay the formation of the oxazolidinone until later in the route.

Chapter 4: Third Generation Strategy to (-)-Agelastatin A

4.1. Modified Retrosynthetic Plan

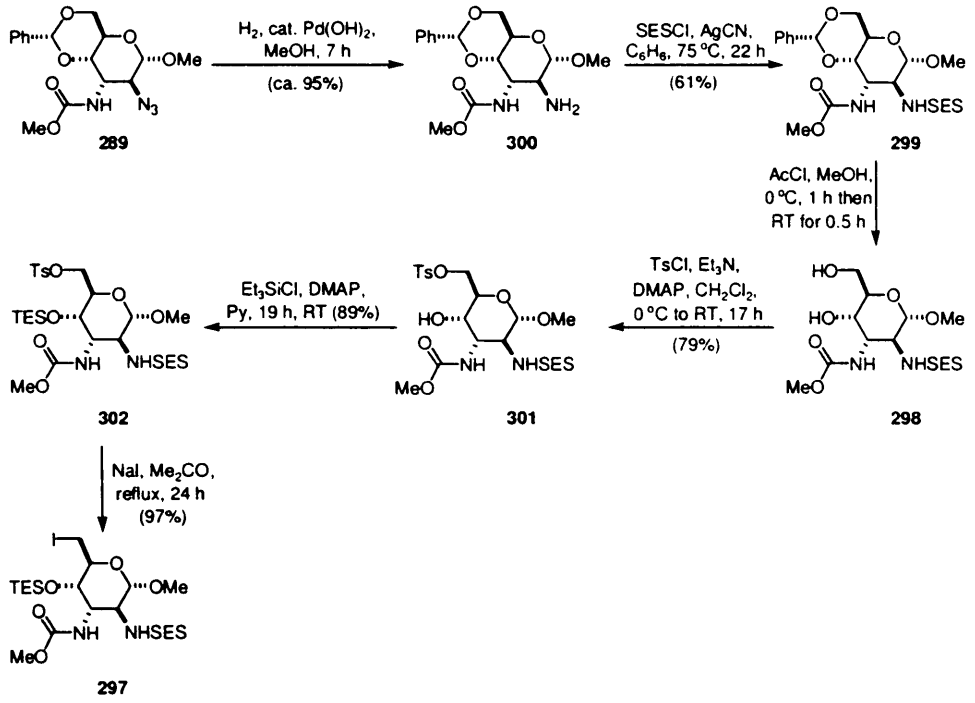
Conceptually, our new route to (-)-agelastatin A would be similar to the last strategy. Now, however, formation of the oxazolidinone in **150** would be delayed until after the RCM step, and we would use a TES group to protect the backbone *O*-atom in **295**. Thus, we would still attempt the preparation of sulfonamide **150**, which would be converted into (-)-agelastatin A using Weinreb's 7-step procedure. A Julia-Kocieński olefination would again be used to create the key RCM diene **295** from aldehyde **296**, and this, in turn, would be synthesised from the 6-iodopyranoside **297** by a Vasella reductive ring-cleavage. Iodide **297** would originate from diol **298**; the latter would be prepared by removal of the benzylidene group from sulfonamide **299**. It would be derived from reduction of the azido group in **289** and sulfonylation of the resulting amine with SES chloride. Azide **289** had already been prepared in the previous route from the Hough-Richardson aziridine.



Scheme 54. Third retrosynthetic strategy

4.2. Implementation of the New Route: An Enantiospecific Formal Total Synthesis of (-)-Agelastatin A

Azide **289**, previously prepared by us in two steps from the Hough-Richardson aziridine, was reductively hydrogenated in methanol in the presence of Pearlman's catalyst (20% $Pd(OH)_2$ on C) to obtain amine **300**. According to ^{1}H-NMR analysis, **300** was obtained in almost pure condition and, as a consequence, was used for the next step without further purification. We next attempted protection the amino group with a SES group.



Scheme 55. Preparation of iodide **261**

The traditional protocol for introducing a SES group, which uses SESCl and Et_3N in DMF, proved disappointing. It provided the desired sulfonamide **299** in a rather modest 23% yield after 11 days, along with other unidentified products (entry 1, Table 1). The sulfonylation protocol employing DABCO (that was previously employed so successfully in the sulfonylation of **286**) afforded **299** in only 14% yield (entry 2). Carpino's biphasic conditions (SESCl, $NaHCO_3$, CH_2Cl_2/H_2O) did not produce any trace of **299** (entry 3). Fortunately, it was found that treatment of **300** with SES chloride in pyridine afforded **299** in 61% yield on a one-gram scale (entry 4). Eventually, an optimised procedure was identified that lowered the amount of valuable SES chloride used, which ran the reaction at a concentration of 0.2 M. Under these conditions, **299** was obtained in 80% yield on a ten-gram scale. However, this protocol was found to be less satisfactory on larger scale, with yields typically being lower, ranging from 50 to 54%. A novel procedure using silver cyanide was therefore investigated. Originally developed for carrying out amidations on base-sensitive peptidic substrates,[113] this process proved successful in a number of situations where electron-deficient or hindered amines were coupled to hindered aminoacid

chlorides.[114,115] This is the first time, however, that this protocol has been applied to the sulfonylation of a primary amine. In our experience, the AgCN method is much more reliable than the base-mediated methods on large scale, since **299** is typically produced in 69% yield when **300**, AgCN, and SESCl (1.5 equiv.) are heated in freshly distilled benzene at reflux under nitrogen.

Table 4. Sulfonylation of amine **300** with SES chloride

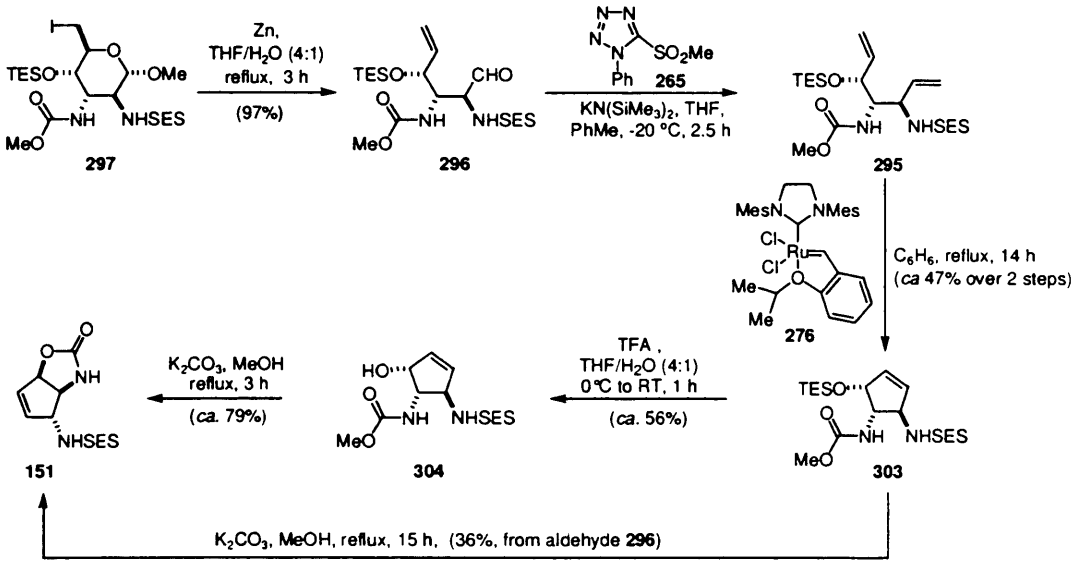
Entry	Conditions	Yield
1	SESCl (1.5 equiv.), Et_3N (5.5 equiv.), DMF (C 0.15 M), RT, 11 d	23 %
2	SESCl (1.5 equiv.), DABCO (3 equiv.), CH_2Cl_2 (C 0.06 M), RT, 18 h	14 %
3	SESCl (2 equiv.), K_2CO_3 (12 equiv.), CH_2Cl_2/H_2O 3:1 (C 0.09 M), RT, 26 h	0 %
4	SESCl (3 equiv.), DMAP (0.1 equiv.), Py (C 0.08 M), RT, 1 h	61 %
5	SESCl (1.5 equiv.), DMAP (0.1 equiv.), Py (C 0.2 M), RT, 20 h	80 %
6	SESCl (1.5 equiv.), AgCN (1.5 equiv.), C_6H_6 (C 0.3 M), reflux, 23 h	69 %

Removal of the benzylidene acetal from **299** was accomplished with anhydrous HCl in methanol; this process proceeded smoothly, affording diol **298** in 85% yield. Regioselective *O*-tosylation of **298** was thereafter achieved in 79% yield by a portionwise addition of TsCl (1.05 equiv.) over several hours to a mixture of **298**, DMAP and Et_3N at 0°C. The TES protecting group was attached to the resulting alcohol **301** without difficulty, by treatment with chlorotriethylsilane in pyridine; **302** was produced in 89% yield. Finally, tosylate **302** was converted into iodide **297** by nucleophilic displacement with sodium iodide in acetone at reflux. This reaction produced **297** in a nearly quantitative yield.

Preparation of the bicyclic oxazolidinone **150** was next attempted (Scheme 56). The Vasella reductive ring-opening of **297** with zinc dust in aqueous THF procured aldehyde **296** in excellent yield (97%). Olefination of **296** with sulfone **265** using Kocieński's protocol effectively produced diene **295**. It was not possible to remove all of the hydroxytetrazole by-product from diene **295** on a preparative scale. However, this impurity did not adversely affect the subsequent Grubbs-Hoveyda ring-closing metathesis reaction, which cleanly converted **295** into the cyclopentene **303**. Yet again, it still proved difficult to remove all of the tetrazole by-product from **303** by SiO_2 flash-chromatography. Therefore, an approximate 47% combined yield over 2 steps is quoted.

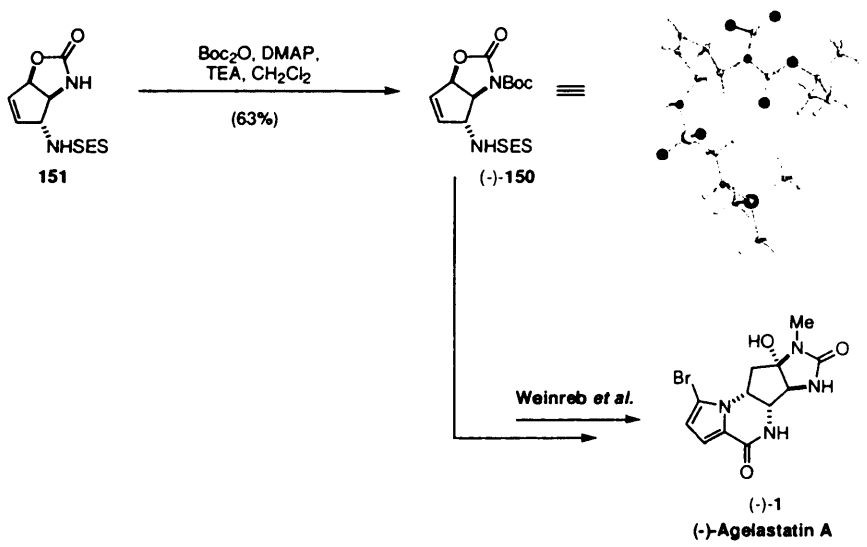
Whilst the *O*-desilylation of **303** with TBAF was problematical, the TES group could be cleaved from **303** with TFA in aqueous THF; **304** was obtained in 56% yield. The latter was converted to the oxazolidinone **151** by potassium carbonate treatment in hot methanol.

However, it was generally more advantageous to obtain the oxazolidinone **151** directly from **303** by heating the latter with K_2CO_3 in MeOH at reflux for 3 hours. An accurate yield of 36% can now be quoted for the pure **151** so obtained from aldehyde **296**.



Scheme 56. Preparation of bicyclic oxazolidione **151**

Now we were then faced with the challenging issue of having to chemoselectively *N*-acylate the oxazolidinone nitrogen in **151** in the presence of the sulfonamide functionality to obtain (-)-**150**. Fortunately, this could be achieved reasonably cleanly and efficiently (in *ca.* 63% yield), by slow addition of a solution of Boc_2O in CH_2Cl_2 to a solution of **151**, DMAP and Et_3N in CH_2Cl_2 (Scheme 57).

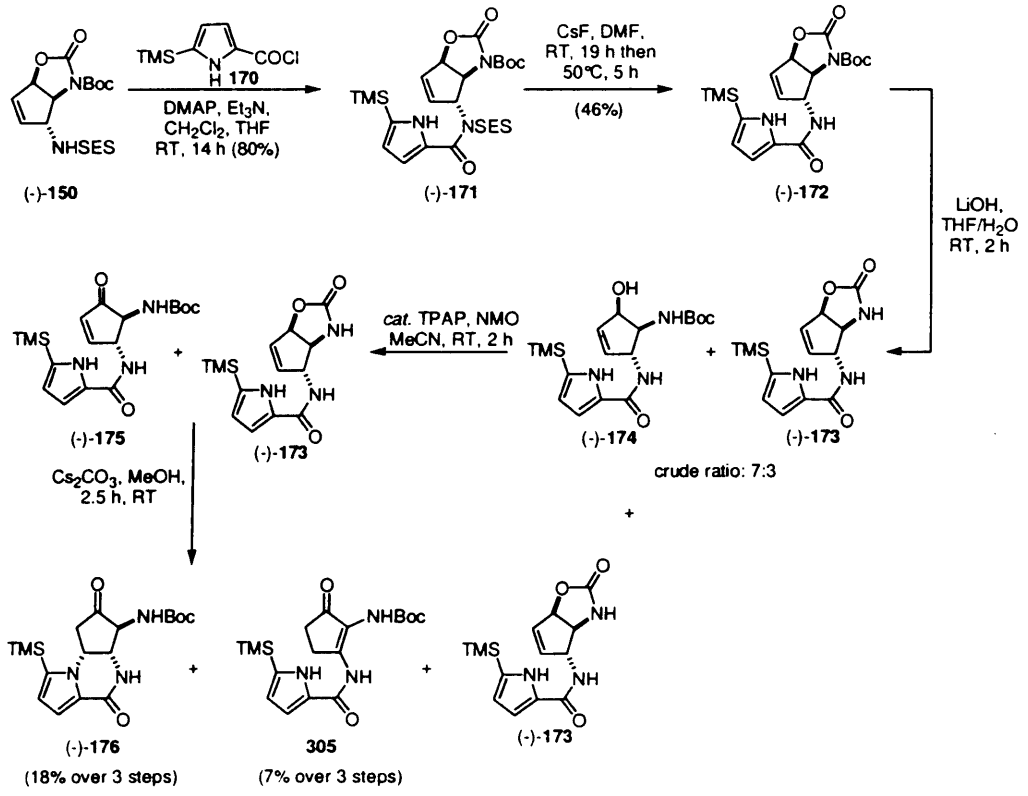


Scheme 57. Completion of the formal total synthesis of (-)-agelastatin A

Racemic **150** had previously featured as an advanced intermediate in Weinreb's total synthesis of (±)-agelastatin A, and the ^{1}H and ^{13}C NMR spectra of our optically pure (-)-**150** matched those recorded by these workers for (±)-**150** in the same solvent. Our enantiopure **150** also had a large negative $[\alpha]_D$ (–88 ° at *c* 0.22 in CH_2Cl_2), and its relative and absolute stereostructure were further confirmed by X-ray crystallography. We had thus completed a formal enantiospecific total synthesis of (-)-agelastatin A.

Chapter 5: A Reinvestigation of Weinreb's Endgame for Agelastatin A

A re-examination of Weinreb's synthetic endgame for racemic agelastatin A has led to us making a number of important process improvements and modifications for the synthesis of the penultimate precursor of the enantiomerically pure natural product (Scheme 58). Although the *N*-acylation of (-)-**150** with acid chloride **170** could be reproduced in a perfectly satisfactory 80% yield (Weinreb quoted a 100% yield in the (±)-system), difficulties were encountered in reproducing the 66% yield they reported for cleavage of the SES group from (-)-**171** with *n*-Bu_4NF in THF. In our hands, the yield of (-)-**172** was typically 30%. A more satisfactory protocol for cleaving the SES group from (-)-**171** exposed it to CsF in DMF at RT for 19 h, prior to heating it at 50 °C for 5 h. The latter procedure furnished the desired product (-)-**172** in an improved 46% yield on a gram-scale.

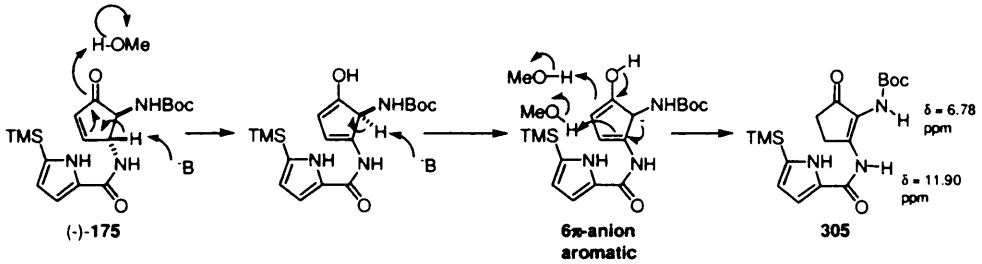


Scheme 58. Formation of the tricyclic core of (-)-agelastatin A

Weinreb's recommended method for accessing **174** regioselectively hydrolyses the oxazolidinone ring in **172** with 8 equiv. LiOH in THF/water (9 :1). Although Weinreb reported that a 4:1 ratio of **174**:**173** was formed, we have observed that a 7:3 mixture of (-)-**174**:(-)-**173** is

typically produced under these conditions; similar results were obtained with 1 equiv. Cs_2CO_3 in MeOH,[116] but the process was now much slower (20 h). Because of the difficulties involved in separating (-)-**174** from (-)-**173** by SiO_2 flash chromatography, we took the chromatographed (but unseparated) mixture forward for the subsequent oxidation step with TPAP and NMO and obtained a mixture of (-)-**175** and (-)-**173**. The TPAP oxidation method generally proved superior to the CrO_3/Py protocol originally reported by Weinreb, it being far easier to work-up, and it using only catalytic quantities of the transition metal oxidant, which is preferable for large-scale work. The separation of (-)-**175** from (-)-**173** by SiO_2 column chromatography again remained very difficult at this stage. The cyclisation of (-)-**175** to (-)-**176** was therefore attempted by exposing the mixture of (-)-**175** and (-)-**173** to Cs_2CO_3 in MeOH, under conditions similar to those originally reported by Weinreb, but involving substantially less Cs_2CO_3. When the reaction was complete, TLC analysis of the crude reaction mixture invariably indicated the presence of three main reaction components: **305**, (-)-**173**, and (-)-**176**, which were now readily separated by SiO_2 flash chromatography; the desired product (-)-**176** was generally isolated in 18% overall yield for the three steps from (-)-**172**.

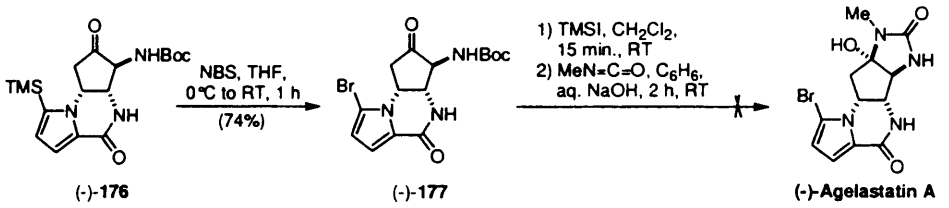
Surprisingly, Weinreb and coworkers did not report the formation of **305** in their cyclisation reaction, yet it was found that this undesired by-product was always produced in around 7% overall yield from (-)-**172**. Evidence for the proposed structure was provided by the 500 MHz ^{1}H-NMR spectrum of **305** in $CDCl_3$ which showed 2 multiplets for two C-H protons at δ 3.33 and 2.47 ppm, and the absence of two olefinic CH protons between 5 and 6 ppm. One possible mechanism (Scheme 59) that accounts for the formation of **305** invokes γ-deprotonation occurring in (-)-**175** to generate a cyclopentadienol or a caesium cyclopentadienolate. The latter then undergoes further deprotonation to produce an aromatic 6-π anionic species that reprotonates to give **305**. The cyclopentenone isomerisation seen here is analogous to the well-known base-mediated prostaglandin A_2 to B_2 rearrangement reported by Roberts and Newton.[117] The extensive n-π conjugation in **305**, and intramolecular H-bonding of the 2 N-H protons is reflected by the low-field position of the two amido N-H protons in the 500 MHz ^{1}H-NMR spectrum of this compound in $CDCl_3$ (Scheme 59). Presumably, the greater degree of conjugation experienced by **305**, and the extra thermodynamic stability of the tetrasubstituted double bond help explain the ease with which this product is formed.



Scheme 59. A possible mechanism for the formation of **305**

The fact that **305** was co-produced in this cyclisation immediately raised concerns about whether compound **176** might be generated as a racemate. The fact that **176** was formed in optically enriched form was indicated by its large negative specific optical rotation in $CHCl_3$ ($[\alpha]_D$ -134° (*c* 0.5 $CHCl_3$)). Clearly, the pyrrole-*N* of (-)-**175** had to be competitively and irreversibly adding to the enone at a rate faster than the γ-deprotonation and α-enolisation/protonation processes were proceeding according to Scheme 59, otherwise racemic **176** (and a more complex mixture) would almost certainly have been the end-result.

The bromination of (-)-**176** provided optically pure (-)-**177** when carried out according to the Weinreb protocol (Scheme 60); the latter was obtained in 74% yield with an $[\alpha]_D$ of -112° in MeOH. Weinreb *et al.* had previously converted (±)-**177** into (±)-agelastatin A by a two-step, one-pot, operation. They used TMSI to remove the Boc group and form a transient trimethylsilylurethane species, that was then cleaved and trapped *in situ* with methyl isocyanate and aqueous sodium hydroxide. This protocol was designed to preclude the formation of a dimeric pyridazine, which could potentially occur by condensation of two α-amino-ketone functionalities.[118,119] In spite of several attempts, no trace of the natural product was ever detected when we used this method. In our hands, addition of new commercial TMSI (obtained from a sealed ampule) under nitrogen to a solution of **177** did lead to the disappearance of starting material and a mixture of slower-moving products was formed according to TLC analysis. However, formation of the urea/hemiaminal ring-system did not occur subsequently when MeNCO and NaOH were added. Although we attempted to isolate the primary amine after deprotection with TMSI or TFA, none of these efforts were successful.



(-)-**176** (-)-**177** (-)-**Agelastatin A**

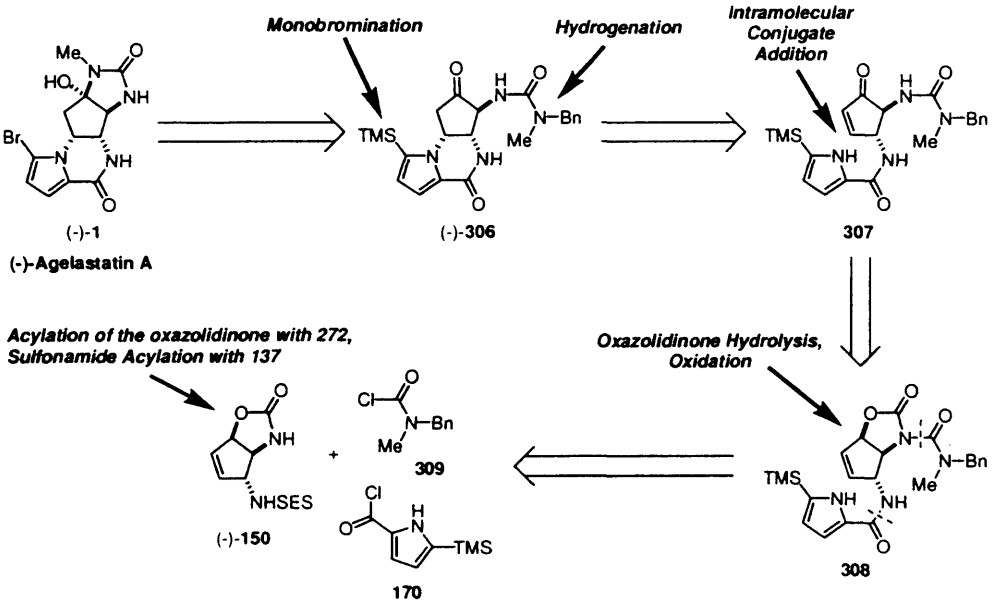
Scheme 60. Our attempts at preparing (-)-agelastatin A from ketone (-)-**176**

In conclusion, a number of process improvements have been made to Weinreb's endgame for securing agelastatin A. However, we were unsuccessful in repeating his final one-pot process for converting (-)-**177** into (-)-agelastatin A. In light of the collective problems we experienced in this endgame, we eventually decided to investigate an alternative method for securing (-)-agelastatin A from (-)-**150**.

Chapter 6: Total Synthesis of (-)-Agelastatin A

6.1. A New Retrosynthetic Strategy for (-)-Agelastatin A that Would Intersect with Oxazolidinone (-)-150

Since we were unable to reproduce Weinreb's last step for preparing (-)-agelastatin A from **177**, we now sought to develop an alternative engame that would avoid the safety issues associated with use of the highly toxic methyl isocyanate for forming the B-ring of the natural product (Scheme 61). Feldman *et al.* had successfully deployed an *N*-benzyl carbamoyl group as a protected precursor of the urea; this cyclised intramolecularly onto the adjacent ketone after hydrogenolysis. It seemed therefore logical to capitalise on their success, and use a similar stratagem in our modified endgame.

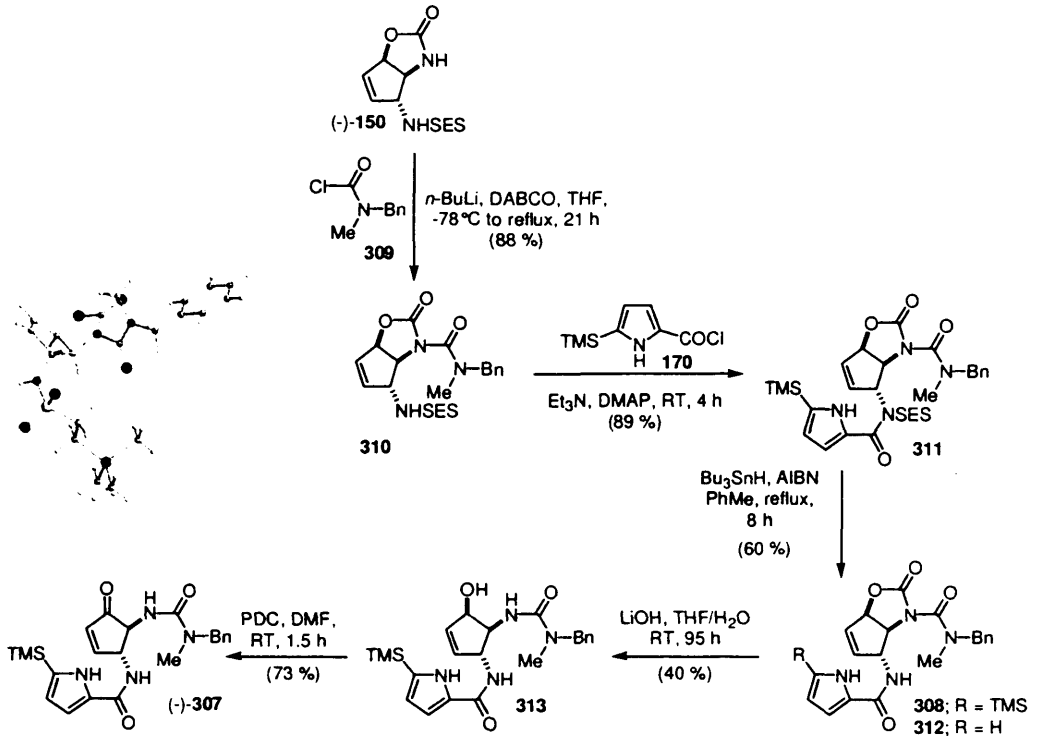


Scheme 61. New endgame for (-)-agelastatin A

The new route that we envisaged would transform oxazolidinone (-)-**150** into the pyrrolo-amide **308** by two regioselective acylations. The first one would be effected on the oxazolidinone nitrogen with carbamoyl chloride **309**; the second one would take place at the sulfonamide functionality. Subsequent removal of the SES group would secure **308**. A base-promoted hydrolysis of the oxazolidinone ring, and an oxidation of the resulting alcohol would furnish **307**. Upon treatment with a suitable base, the latter would undergo an intramolecular Michael-type addition of the pyrrole nitrogen onto the double bond of the unsaturated ketone and produce (-)-**306**. Hydrogenolysis of the *N*-benzyl group and monobromination of the pyrrole ring would then hopefully complete the total synthesis of (-)-**1**.

6.2. Implementation of the New Endgame Strategy

The new endgame started with the regioselective *N*-carbamoylation of oxazolidinone (-)-**150** with carbamoyl chloride **309**.[81] This was conveniently achieved by using a combination of *n*-BuLi and DABCO as the bases. Thus, (-)-**150** was treated with *n*-BuLi at low temperature, and carbamoyl chloride **309** was added. The mixture was heated at reflux for 4 h, and DABCO (3 equiv.) was then added and the heating continued for 18 h. The regioselectivity of this reaction can certainly be explained by the formation of a *N*-lithiated species which is stabilised by coordination of the oxygen lone pairs of the adjacent sulfonamide group. The structure of the carbamoyl oxazolidinone **310** was subsequently confirmed by X-Ray analysis. A second *N*-acylation with pyrrole acid chloride **170**, triethylamine and DMAP produced the desired pyrrolocarboxamide **311** in 89% yield. As before, syringe pump addition of a solution of the acid chloride in CH_2Cl_2 to a solution of sulfonamide **310** was required to perform this acylation (Weinreb's procedure).

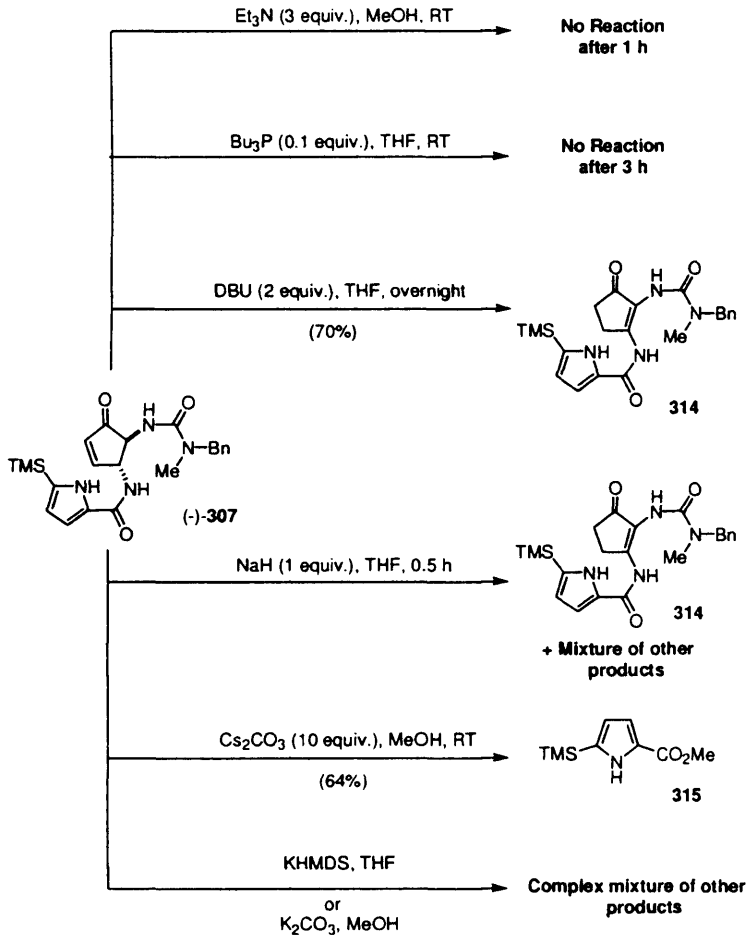


Scheme 62. Preparation of cyclopentenone (-)-**307**

Although fluoride-induced cleavage of the SES group in **311**, using 1 equiv. TBAF in THF at 0°C, afforded **308** in a poor yield (34%), we found that this deprotection could be effected much more efficiently by using Bu_3SnH and AIBN in PhMe at reflux. The free pyrroloamide was typically obtained in 60% yield. This procedure was originally developed by Smith *et al.* for the desulfonylation of multifunctional β-keto-phenylsulfones under neutral conditions.[120] This method was subsequently applied to the deprotection of arylsulfonylated

amides by Parsons.[121] To our knowledge, this is the first time that a SES group has been reductively removed from an amide nitrogen by Bu_3SnH under free radical conditions. A small amount of the *C*-desilylated product **312** (up to 7%) was also sometimes encountered in this Bu_3SnH reduction depending on its overall duration.

Our next objective was to hydrolyse the oxazolidinone ring of **308** whilst leaving the urethane unit intact. Although this reaction could be accomplished cleanly with aq. LiOH in THF at room temperature, it did required long reaction times (128 h) to deliver workable yields of product. In this regard, the desired allylic alcohol **313** could usually be isolated in 40% yield along with 48% of **308** which was then recycled. Based on the quantity of **308** that was typically recovered, the yield of **313** was calculated to be 77%. Evidences for the success of this reaction was given by the appearance of an OH streching band at 3312 cm^{-1} on the infra-red spectrum of **313**. Moreover, 125 MHz ^{13}C-NMR analysis of **313** in $CDCl_3$ showed disappearance of the oxazolidinone carbonyl as well as the downfield shift of the urethane carbonyl to 159 ppm. Subsequent oxidation of alcohol **313** with the TPAP/NMO system in acetonitrile produced enone (-)-**307** in 66% yield. However, it was found that pyridinium dichromate was slightly more effective in this capacity, affording (-)-**307** in a highly reproducible 73% yield.



Scheme 63. Attempts at cyclising enone (-)-**307**

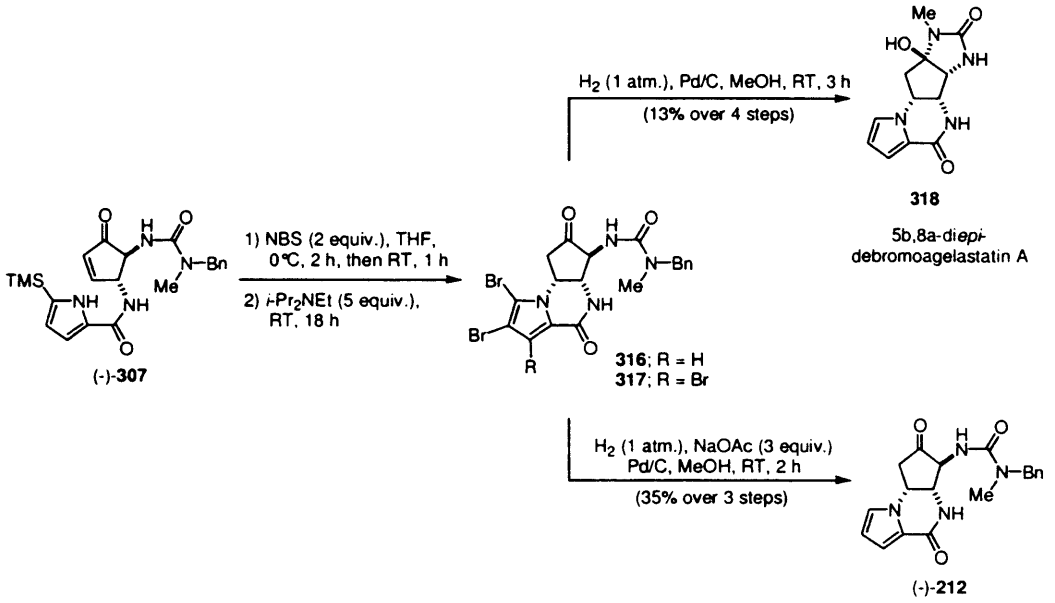
We next investigated the the base-mediated ring-closure of enone (-)-**307** to secure ketone (-)-**306**. Et_3N in MeOH, or 10 mol% Bu_3P in THF,[122] were completely ineffective at mediating this cyclisation, enone **307** being recovered untouched in either case. When enone **307** was treated with 2 equiv. DBU in THF at room temperature, the rearranged enone **314** was produced in 70% yield. Presumably, a rearrangement similar to the one previously observed during the reinvestigation of Weinreb's endgame took place. Sodium hydride was also investigated for effecting the desired ring-closure of **307**, but this base failed to deliver the cyclised ketone **306**, and a complex mixture of compounds was produced, including the rearranged cyclopentenone **314**. Potassium hexamethyldisilazide in THF likewise gave rise to complicated reaction mixtures, as did K_2CO_3 in MeOH. Surprisingly, Cs_2CO_3 in MeOH produced **315** as the only readily isolable reaction product in 64% yield, along with other decomposition products.

In light of these failures, several Brønsted and Lewis acids were surveyed for their ability to instigate the desired cyclisation. PPTS (5 equiv.) in THF and MeOH was initially screened in this capacity. Unfortunately, this led to the pyrrole TMS of **307** being replaced by hydrogen. The latter product was also formed when TMSOTf (1.1 equiv.) was used to activate enone **307** in methanol; it was co-produced with **314**. Given all these disappointments, a step backwards was taken, and the Swern oxidation and *in situ* cyclisation of **307** was attempted under conditions analogous to those reported by Feldman and co-workers on their related system.[75] With our substrate, this led to a 16% isolated yield of **306**, 20% yield of enone **314**, and a 62% recovery of **307**.

3. Completion of the (-)-Agelastatin A Total Synthesis: A Lesson From Nature

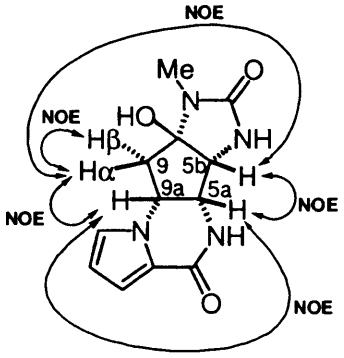
At about this time, we happened to again read the Potier/Al Mourabit paper on the possible biosynthesis of (-)-agelastatin A,[15] and a key feature of their proposal was the internal Michael-type addition of a bromopyrrole in intermediate **13** (Scheme 3) for ABC ring-assembly. It occurred to us that if Nature could accomplish the same type of reaction under near neutral conditions, that perhaps the increased acidity of the bromopyrrole-NH could hold the key to ultimate success in our own synthetic venture. We reasoned that because Et_3N in MeOH had left enone **307** intact, after several hours of exposure, that we might be able to bring about cyclisation under similar conditions, if we could lower the pKa of the pyrrole nitrogen in **307** through chemoselective bromination. Accordingly, **307** was reacted with 2 equiv. of *N*-bromosuccinimide in THF for 3 h, in the expectation that a single 2,3-dibromopyrrole would form, whose pKa would be significantly lower. To our surprise, a complex mixture of mono-, di-, and tri-bromo pyrroles arose on TLC, and none of the starting enone remained. Therefore, rather than attempting to purify the individual products, Hunig's base (5 equiv.) was added directly to the reaction mixture to promote the required intramolecular Michael-type addition.

The only component of this mixture that was obtained in reasonably pure condition was the tribromopyrrole **317**. Use of 3 equiv. of NBS for the bromination did not increase the amount of **317** that was formed, but instead, caused over-bromination and significant product decomposition.



Scheme 64. Conjugate intramolecular addition of enone (-)-**270** and subsequent debromination

The crude mixture from the 2 equiv. of NBS reaction/Hünig's base cyclisation was then extractively worked-up and directly submitted to debromination using a catalytic amount of 10% Pd/C in MeOH in the presence of AcONa (3 equiv.). The success of this conversion was apparent from the presence of three aromatic protons at δ 6.78, 6.25 and 6.86 ppm in the 500 MHz ^{1}H-NMR spectrum of **212** in $CDCl_3$. The desired ketone (-)-**212** was readily isolated by chromatography in 35% yield over 3 steps. Initially, the reaction was performed without the inclusion of AcONa. It was expected that the HBr liberated during the debromination reaction would actually promote the *N*-debenzylation of **212** to form debromoagelastatin A directly in one operation. In fact, 5b,8a-di*epi*-debromoagelastatin A (**318**) was formed instead; it was isolated in 13% yield over 3 steps. The structure of this epimer was confirmed by a 500 MHz 2D NMR-NOESY experiment in CD_3OD, which showed a strong nuclear Overhauser effect (NOE) effect between H(5a) and H(5b) (Figure 8). Moreover, the 500 MHz ^{1}H-NMR spectrum of **318** in CD_3OD showed a ^3J coupling constant between H(5a) and H(5b) of 7.3 Hz, which is consistent with a *cis* relationship between these two protons (this coupling is absent in the spectrum of debromoagelastatin A where these protons are in a *trans* relationship). It is likely that the epimerisation of **316** at C(5b) (agelastatin numbering) which led to **318** is promoted by the acid liberated during the debromination.



318
epi-debromoagelastatin A

Figure 8. NOE effects in 5b,8a-diepidebromoagelastatin A

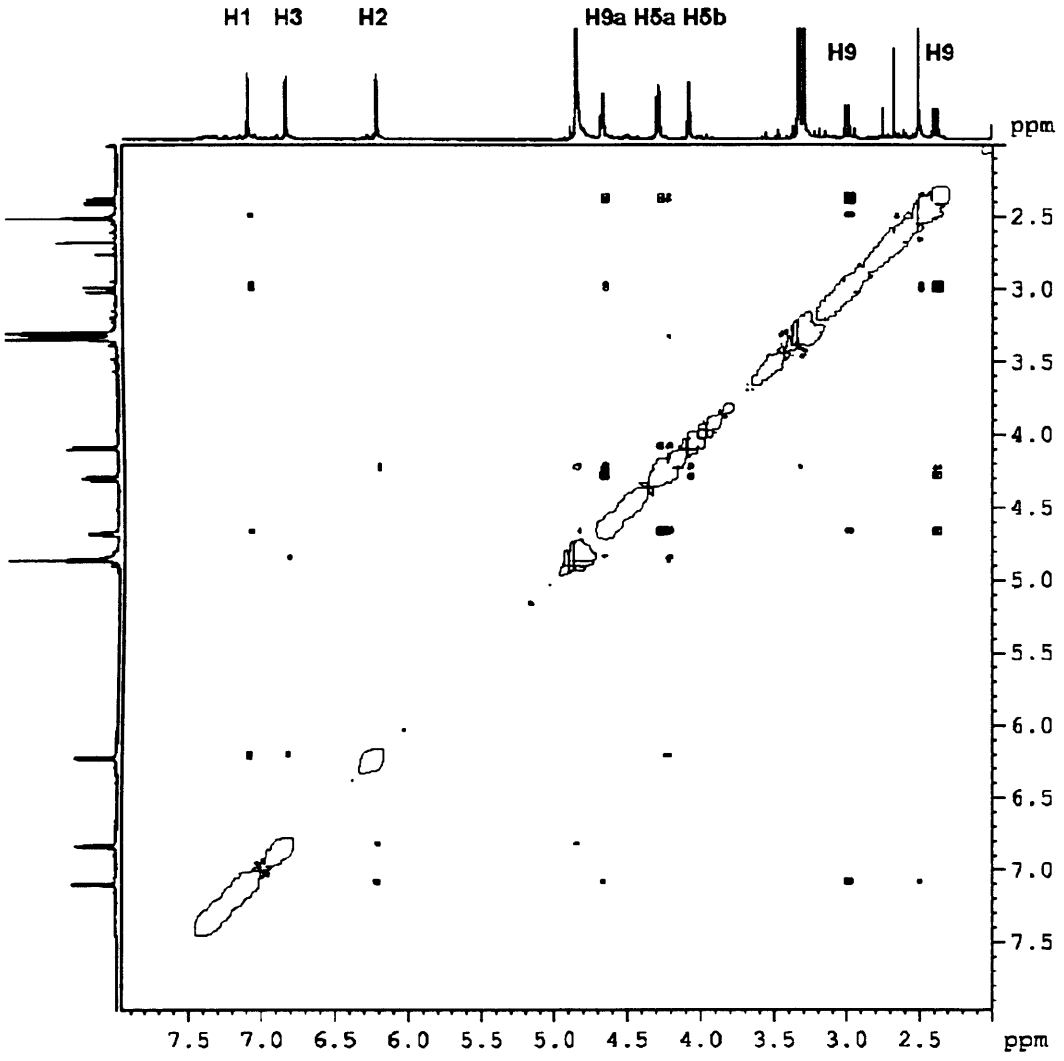
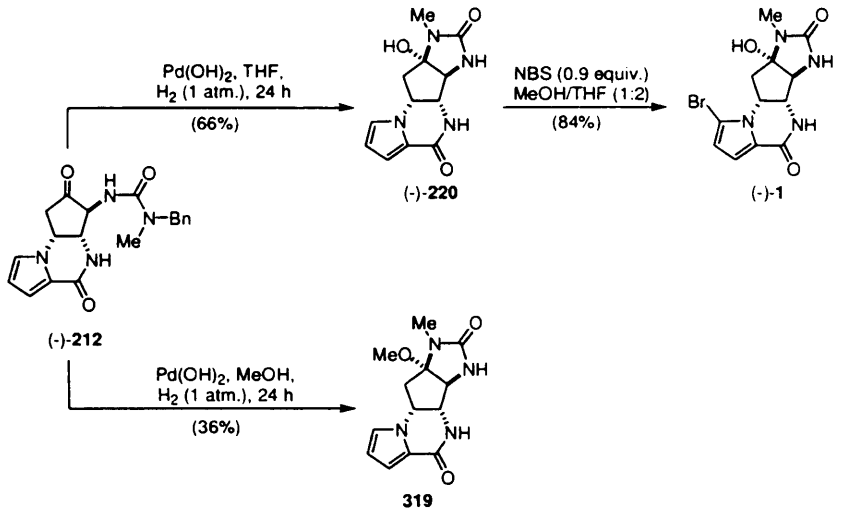


Figure 9. 500 MHz 1H NOESY spectrum of **318** in CD_3OD

Initially, the *N*-debenzylation of (-)-**212** by catalytic hydrogenation was attempted using Pearlman's catalyst (20% $Pd(OH)_2/C$) in methanol (Scheme 65). Unfortunately, this led to the formation of methyl acetal **319** in a 36% yield. Conducting this reaction in THF, however, completely avoided this undesired reaction, and afforded debromoagelastatin A (-)-**220** in 66% yield. Regioselective mono-bromination of **220** with NBS in a 1:2 mixture of MeOH/THF according to the protocol described by Feldman *et al.* provided (-)-agelastatin A (-)-**1** in 84% yield.



Scheme 65. Removal of the *N*-benzyl group and subsequent bromination

Via the above route, about 220 mg of (-)-Agelastatin A has been prepared, and this is currently being evalated in more detail as an antitumour agent. More details of the biology are presented in Chapter 7.

Chapter 7. Evaluation of the Biological Properties of (-)-Agelastatin A

7.1. Growth Inhibition Assays

The *in vitro* potency of (-)-agelastatin A as an antitumour agent was compared with cisplatin through growth inhibition assays conducted against a panel of 15 human tumour cell lines. These results were obtained by Quintiles Ltd. (Edinburgh, U.K.), the pharmaceutical services company.

Table 5. Comparative *in vitro* antitumour profile of (-)-agelastatin A

Human Tumour Cell Line	(-)-Agelastatin A Mean IC_{50} (μM)	Cisplatin Mean IC_{50} (μM)
NCI-H460 (Lung)	0.195	0.832
LoVo (Colon)	0.975	3.315
DLD-1 (Colon)	0.398	2.362
HCT116 (Colon)	0.344	2.249
HT-29 (Colon)	0.670	4.736
ACHN (Renal)	2.133	1.057
MDAM B435s (Breast)	0.497	5.627
MES-SA (Uterine)	0.162	0.285
MES-SA/Dx5 (Uterine)	8.420	5.826
HepG2 (Hepatic)	0.846	3.300
DU145 (Prostate)	0.701	1.051
BxPC-3 (Pancreatic)	0.414	2.409
AsPC-1 (Pancreatic)	0.642	6.151
RT112/84 (Bladder)	0.234	3.793
SK-MEL-5 (Melanoma)	0.485	6.393

Experimentally, the cells were plated into 96-well plates at an appropriate cell density relating to the doubling time of each cell line, and the exposure time required in the study. The cells were incubated overnight in order to allow the cells to adhere. The cells were then treated with test substance at a range of concentrations. After incubating for 72 hours, the cells were stained, and the plates were read at the appropriate wavelength on a plate reader, the

absorbance for each well relating to the number of cells present. From there, the Quintiles group determined and compared the potency of the test substances, by calculating an IC_{50} value (the concentration of test substance that inhibits 50% of cell growth compared with control cells) from a computer-generated concentration-response curve. The data they obtained are shown above (Table 5). The results show that (-)-agelastatin A is between 1.5 and 16 times more potent than cisplatin at inhibiting cancer cell growth in all but two cancer cell lines.

From these results, a particular cell line, HCT116, was selected for *in vivo* human mouse xenograft studies. The primary purpose of this study was to evaluate toxicity rather than demonstrate efficacy, although some reduction in tumour growth was noted. When (-)-agelastatin A was administered intraperitoneally at 2.5 mg/kg/day for 4 successive days to a 10 mouse cohort that had been intraperitoneally inoculated with HCT-116 solid human carcinoma, it produced a 31% mean inhibition of growth by day 4 without toxicity. Although a 30% inhibition of tumour growth was maintained at day 7, by day 15, a 15% inhibition of tumour growth was apparent, which declined to 10% inhibition by day 20. The results suggest that (-)-agelastatin A is cytostatic rather than cytotoxic, and that it is well tolerated at this dosage. Further antitumour testing will be performed to assess the antitumour effects of continuous dosing of (-)-agelastatin A to mice.

7.2. Inhibition of GSK-3β

During their screening of the inhibitory effects of (-)-agelastatin A on certain kinases of neurological therapeutic significance, Meijer found that it inhibited GSK-3β (glycogen synthase kinase-3β) with an IC_{50} of 12 μM, although it did not inhibit the related kinases, CK1 (casein kinase 1), CDK1/cyclin B, (cyclin dependent kinase 5/cyclin B) or CDK5/p25.[123] GSK-3β is a ubiquitously expressed multifunctional serine/threonine kinase found in all eukaryotes. It was first isolated as an enzyme capable of phosphorylating and inhibiting the enzyme glycogen synthase.[124] Beyond its role in glycogen metabolism, GSK-3β acts as a downstream regulatory switch that regulates the output of numerous signalling pathways initiated by diverse stimuli.[125] These pathways are involved in a wide range of cellular processes ranging from glycogen metabolism to cell cycle regulation and proliferation. Given its potential involvement in many pathophysiological processes when deregulated, GSK-3β has emerged as a very promising therapeutic target, particularly when its upregulation may be linked to pathology.[126] Amongst these diseases, non-insulin-dependent diabetes mellitus and neurodegenerative disorders such as Alzheimer disease are the most prominent.

Chapter 7. Evaluation of the Biological Properties of (-)-Agelastatin A

A sample of (-)-agelastatin A that we had prepared by total synthesis was tested against GSK3β to confirm the original report that it is an inhibitor of GSK-3β. This assay was very kindly performed by Prof Adrian Harwood and Dr Jonathan Ryves at the Biology Department, UCL. They obtained an IC_{50} of 6.5 μM for our material, which is consistent with the reported IC_{50} of 12 μM obtained by Meijer. Their results are depicted below (Figure 10).

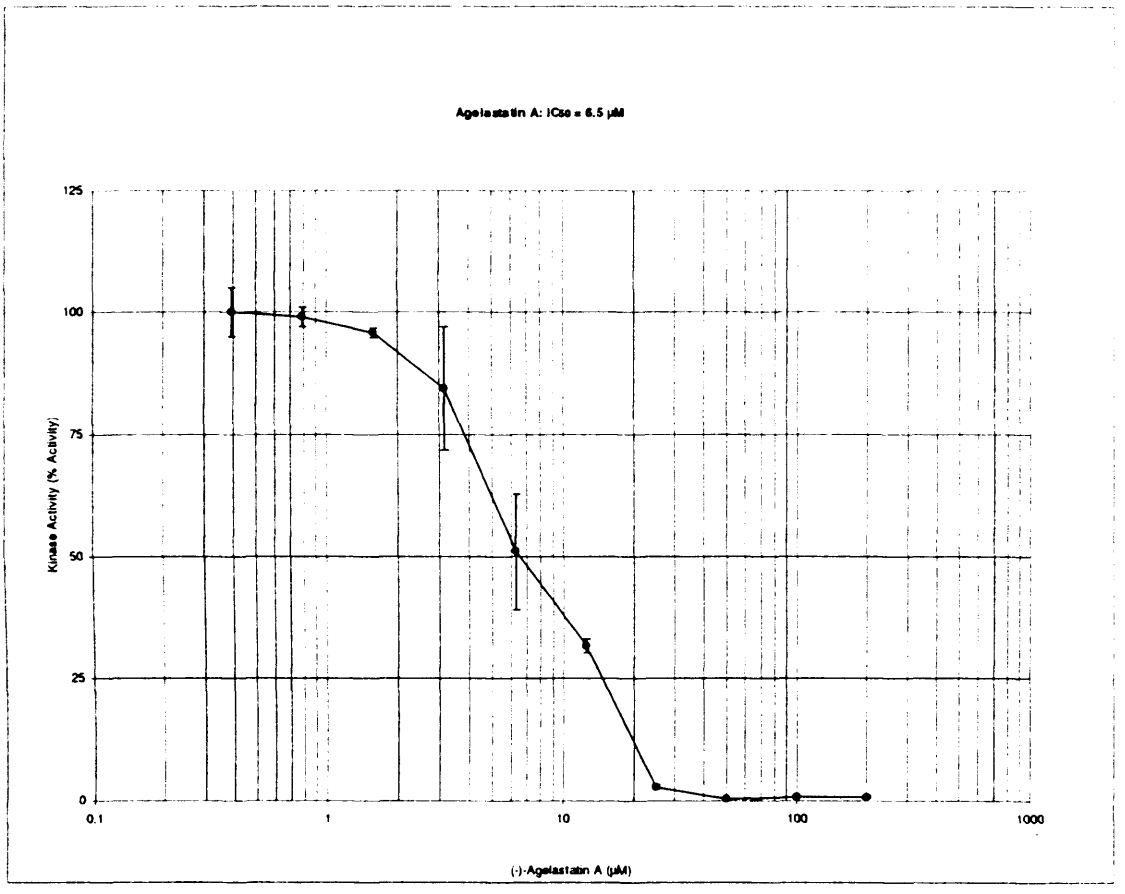


Figure 10. Inhibition of GSK3β by (-)-Agelastatin A

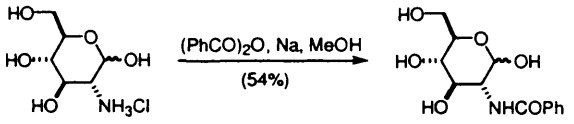
As a consequence of this preliminary biological evaluation, we have confirmed the great potential of (-)-agelastatin A as a human antitumour drug, and we have also confirmed that it is a potentially important new lead for the design of novel GSK-3β inhibitors.

Chapter 8: Experimental

Materials and methods

Dichloromethane, toluene, benzene, acetonitrile and triethylamine were freshly distilled from CaH_2 under nitrogen, diethyl ether and THF were freshly distilled from sodium metal under nitrogen. Thin-layer chromatography was performed on pre-coated glass-backed plates (Merck Kieselgel 60 F_{254}), and visualised by staining with anisaldehyde/H_2SO_4/AcOH in EtOH and heating. Flash column chromatography was carried out on Sorbisil C60 40/60A (230-400 Mesh) silica gel. All ^{1}H-NMR spectra were recorded on a Bruker AMX 400 (400 MHz) or a Bruker AMX 500 (500 MHz) spectrometer. Chemical shifts are reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 7.24 ppm, DMSO-d_6 : δ 2.49 ppm, CD_3OD : δ 3.30 ppm, C_6D_6 : δ 6.15 ppm, Tol-d_8 : δ 7.24 ppm). Data are reported as follows : chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant and assignment. The coupling constants were not averaged. All ^{13}C-NMR spectra were recorded on a Bruker AMX 400 (100 MHz) or a Bruker AMX 500 (125 MHz) spectrometer. Chemical shifts are reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 77 ppm, DMSO-d_6 : δ 39.5 ppm, CD_3OD : δ 49.0 ppm, C_6D_6 : δ 128.0 ppm, Tol-d_8 : δ 20.4 ppm). Infrared spectra (IR) were recorded on a Perkin Elmer 1600 Series FTIR spectrometer, with ν_{max} in inverse centimeters. Bands are characterised as broad (br), strong (s), medium (m) or weak (w). High resolution mass-spectra (HMRS) were measured by the UCL Chemistry Department Mass Spectrometry Service on a VG Analytical 70S instrument. Optical rotations were measured on a Polaar 2000 Automatic polarimeter.

N-benzoyl-D-glucosamine (236)[89]

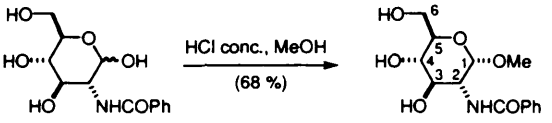


235 D-Glucosamine hydrochloride

236

To a solution of sodium (38.4 g, 1.67 mol) in methanol (3.6 L) was added D-glucosamine hydrochloride (300 g, 1.39 mol) under gentle stirring at room temperature. Sodium chloride separated, and after 15 minutes, the suspension was filtered. To the clear filtrate under mechanical stirring was added benzoic anhydride (441 g, 1.95 mol) in small portions over 15 min. After the end of the addition, the mixture was stirred at room temperature for 5 hours, and stored at 5°C for 3 days to allow the product to crystallise. The crystals were filtered off, washed with methanol, Et_2O and dried under high vacuum, affording **236** (204 g, 54%) as a white solid. M.p. 208-209°C (Lit.[89] m.p. 204-206°C).

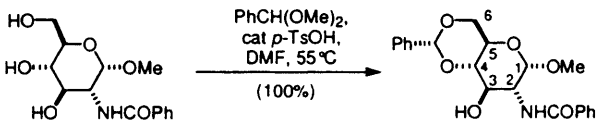
Methyl 2-benzamido-2-deoxy-α-D-gluco-pyranoside (237)[88]



236 **237**

N-Benzoyl-D-glucosamine **236** (204 g, 720 mmol) was suspended in methanol (1.2 L), and conc. HCl (27 mL) was added. The mixture was reluxed for 28 h. After cooling to room temperature, the product was crystallised from the reaction mixture by addition of Et_2O (2 L) and Petrol (1L). The crystals were filtered off, and washed with Et_2O, yielding **237** (145 g, 68%) as a white solid. M.p. 225-227°C (Lit.[88] m.p. 224-227°C); ^{1}H-NMR (500 MHz, 298 K, DMSO-d_6) δ 8.14 (d, *J* = 7.7 Hz, 1 H, arom.), 7.84 (d, *J* = 7.3 Hz, 2 H, arom.), 7.51 (t, *J* = 7.4 Hz, 1 H, arom.), 7.45 (t, *J* = 7.7 Hz, 2 H, arom.), 5.03 (d, *J* = 5.4 Hz, 1 H, C(4)-OH), 4.77 (d, *J* = 5.7 Hz, 1 H, C(3)-OH), 4.69 (d, *J* = 3.5 Hz, 1 H, H1), 4.55 (t, *J* = 6.0 Hz, 1 H, C(6)-OH), 3.87 (ddd, *J* = 10.9, 7.8, 3.6 Hz, 1 H, H2), 3.70 (m, 1 H, H3), 3.67 (ddd, *J* = 9.3, 5.7, 1.9 Hz, 1 H, H6), 3.50 (ddd, *J* = 11.9, 6.0, 5.8 Hz, 1 H, H6), 3.37 (ddd, *J* = 9.8, 5.6, 1.9 Hz, 1 H, H5), 3.24 (s, 3 H, OMe), 3.19 (m, 1 H, H4); ^{13}C-NMR (125 MHz, 298 K, DMSO-d_6) δ 166.5 (C=O), 134.3 (arom.), 131.2 (arom.), 128.1 (arom.), 127.4 (arom.), 97.8 (C1), 72.8 (C5), 70.8 (C4), 70.3 (C3), 60.9 (C6), 54.8 (C2), 54.4 (OMe); HRMS Calcd for $C_{14}H_{20}NO_6$ $(M+H)^+$: *m/z* 298.12906. Found: *m/z* 298.12772.

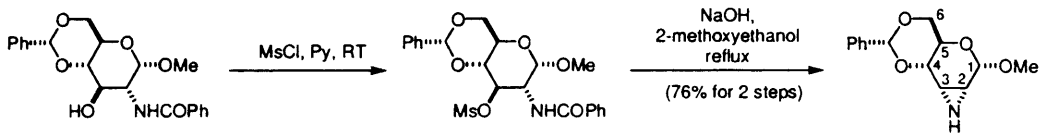
Methyl 2-benzamido-4,6-*O*-benzylidene-2-deoxy-α-D-gluco-pyranoside (238)[88]



237 238

Methyl 2-benzamido-2-deoxy-α-D-gluco-pyranoside **237** (145 g, 488 mmol) was dissolved in DMF (2.2 L). Benzaldehyde dimethylacetal (110 mL, 732 mmol) was added, followed by *p*-toluenesulfonic acid (19 g, 97.5 mmol). The mixture was distilled on a rotary evaporator under vacuum (29 mm Hg) at 55°C. After 5.5 h, the slurry was cooled to room temperature, and washed with absolute ethanol. The crystals were further washed with Et_2O, and dried under high vacuum overnight, yielding the title compound **238** (190 g, 100%) as a white solid. M.p. 237-238°C (Lit.[88] m.p. 239-245°C); ^{1}H-NMR (500 MHz, 298 K, $CDCl_3$) δ 7.79 (d, *J* = 7.2 Hz, 2 H, arom.), 7.53-7.33 (m, 8 H, arom), 6.52 (d, *J* = 8.6 Hz, 1 H, NH), 5.57 (s, 1 H, PhC<u>H</u>), 4.82 (d, *J* = 3.8 Hz, 1 H, H1), 4.43 (ddd, *J* = 9.9, 9.0, 3.9 Hz, 1 H, H2), 4.29 (dd, *J* = 9.3, 3.9 Hz, 1 H, H6), 4.01 (dd, *J* = 9.6, 9.6 Hz, 1 H, H3), 3.81 (m, 1 H, H5), 3.78 (dd, *J* = 10.2, 9.4 Hz, 1 H, H6), 3.64 (t, *J* = 9.1 Hz, 1H, H4), 3.42 (s, 3H, OC<u>H</u>$_3$); ^{13}C-NMR (125 MHz, 298 K, $CDCl_3$) δ 168.5 (C=O), 137.1 (arom.), 133.6 (arom.), 132.0 (arom.), 129.2 (arom.), 128.6 (arom.), 128.3 (arom.), 127.2 (arom.), 126.3 (arom.), 102.0 (Ph<u>C</u>H-), 98.9 (C1), 82.1 (C4), 70.8 (C3), 68.8 (C6), 62.4 (C5), 55.4 (-OCH_3), 54.4 (C2); HRMS Calcd for $C_{21}H_{24}NO_6$ $(M+H)^+$: *m/z* 386.16035. Found: *m/z* 386.16076.

Methyl 4,6-*O*-benzylidene-2,3-dideoxy-2,3-epimino-α-D-allo-pyranoside (234)[90]



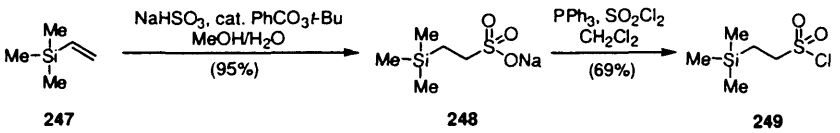
238 239 234
Hough-Richardson Aziridine

MsCl (120 mL, 1.55 mol) was added dropwise to a stirred solution of alcohol **238** (200 g, 0.516 mol) in pyridine (2 L) at 0°C. After the end of the addition, the mixture was stirred at 0°C for 1 h, and at room temperature for 2 hours. The mixture was then carefuly poured into ice/water (3L) to precipitate the mesylate. The crystals were filtered off, and thoroughly washed with water. The crystals were dried by azeotroping any remaining water with toluene. A small sample was purified by recrystallisation from hot ethanol to give **239** as white needles. M.p. 197-198°C (Lit.[90] m.p. 207.5-208.5°C); ^{1}H-NMR (500 MHz, 298 K, $CDCl_3$) δ 7.84 (d, *J* = 7.2 Hz,

2 H, arom.), 7.50-7.35 (m, 8 H, arom.), 6.62 (d, J = 8.8, 1H, NH), 5.58 (s, 1 H, PhC<u>H</u>-), 4.96 (d, J = 3.6 Hz, 1 H, H1), 4.93 (dd, J = 10.1, 9.9 Hz, 1 H, H3), 4.59 (ddd, J = 9.5, 3.6, 1.5 Hz, 1 H, H2), 4.33 (dd, J = 10.3, 4.5 Hz, 1H, H6), 3.94-3.78 (m, 3 H, H4, H5 and H6), 3.38 (s, 3H, -OCH_3), 2.93 (s, 3H, $SO_2C\underline{H}_3$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.5 (C=O), 136.6 (arom.), 133.7 (arom.), 131.8 (arom.), 129.3 (arom.), 128.6 (arom.), 128.4 (arom.), 127.3 (arom.), 125.9 (arom.), 101.8 (Ph<u>C</u>H-), 99.1 (C1), 79.0 (C4), 78.1 (C3), 68.8 (C6), 63.0 (C5), 55.6 (-O<u>C</u>H_3), 52.7 (C2), 38.5 ($SO_2\underline{C}H_3$); HRMS Calcd for $C_{22}H_{26}NO_8S$ $(M+H)^+$: *m/z* 464.13791. Found: *m/z* 464.13743.

The crude mesylate **239** was dissolved in a mixture of 2-methoxyethanol (1.9 L) and water (100 mL). Sodium hydroxide (124 g, 3.10 mol) was then added, and the mixture was refluxed. After 4 h, the solution was cooled down to room temperature, and diluted with water (3 L). The product was extracted with chloroform (6 x 400 mL). The combined organic layer was washed with water (1 L), brine (500 mL), dried ($MgSO_4$), and treated with decolourising charcoal. After filtration, the solution was concentrated *in vacuo*, and the brown solid obtained was purified by recrystallisation in a hot mixture of AcOEt/Petrol, yielding aziridine **234** (104 g, 76% combined yield for 2 steps) as a white solid. $[\alpha]_D$ +148.2 ° (*c* 1, CH_3Cl_3), Lit.[90] $[\alpha]_D$ +147 ° (*c* 1, CH_3Cl_3); IR (KBr) 3301 (s), 3225 (w), 3008 (m), 2924 (m), 28996 (m), 2838 (w), 1635 (w), 1539 (w), 1457 (w), 1393 (m), 1316 (w), 1290 (w), 1245 (w), 1218 (w), 1106 (s), 1070 (s), 1015 (s), 961 (m), 936 (m), 891 (m), 753 (m), 695 (m), 620 (w); ^{1}H-NMR (500 MHz, $CDCl_3$, 298 K) δ 7.50-7.45 (m, 2 H, arom.), 7.37-7.29 (m, 3H, arom.), 5.56 (s, 1 H, PhC<u>H</u>-), 4.88 (d, J = 3.8, 1 H, H1), 4.20 (dd, J = 10.1 Hz, 5.0 Hz, 1 H, H6), 3.98 (br s, 1 H, H5), 3.89 (br d, J = 8.5 Hz, 1 H, H4), 3.64 (dd, J = 10.4, 10.4 Hz, 1 H, H6), 3.42 (s, 3 H, -O<u>C</u>H_3), 2.71 (m, 2 H, H2 and H3); ^{13}C-NMR (125 MHz, $CDCl_3$, 298 K) δ 137.4 (arom.), 129.1 (arom.), 128.3 (arom.), 102.6 (Ph<u>C</u>H-), 95.8 (C1), 77.9 (C4), 69.1 (C6), 59.4(C5), 55.5 (-O<u>C</u>H_3), 33.0 (C3), 30.1 (C2); HRMS Calcd for $C_{14}H_{18}NO_4$ $(M+H)^+$: *m/z* 264.12358. Found: *m/z* 264.12312.

β-Trimethylsilylethanesulfonyl chloride (249)[69,92]

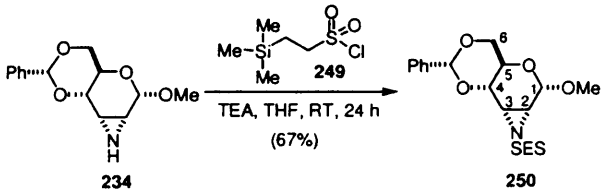


Sodium 2-trimethylsilylethanesulfonate (248).[69] A solution of sodium bisulfite (143 g, 1.37 mol) in water (250 mL) was slowly added to a solution of vinyltrimethylsilane (68.4 g, 0.683 mol) in methanol (250 mL). *tert*-Butyl peroxybenzoate (2.6 mL, 0.0137 mol) was then added, and the mixture was heated at 60°C (temperature of the bath) for 48 hours. After cooling to

room temperature, the mixture was filtered and concentrated under vacuum. The remaining water was removed by azeotroping the mixture with methanol (3 x 250 mL). The resulting solid was extracted with 1 L of methanol, which was concentrated to dryness to afford a white solid. This solid was dried under high vacuum for 1 day to give 113.6 (81 %) of the title compound. ^{1}H-NMR (500 MHz, $CDCl_3$, 298 K) δ 2.73-2.70 (m, 2 H), 1.04-1.01 (m, 2 H), 0.03 (s, 9 H); ^{13}C-NMR (125 MHz, $CDCl_3$, 298 K) δ 48.1, 12.7, -2.0.

2-Trimethylsilylethanesulfonyl chloride (249).[92] Sulfuryl chloride (140 mL, 1.74 mol) was added dropwise to a stirred solution of triphenylphosphine (414,4 g, 1.58 mol) in dichloromethane (2 L) at 0°C. After 2 hours, The crude sodium 2-trimethylsilylethanesulfonate (110.2 g, 0.790 mol) was added in portions. After the addition was complete, the cold bath was removed and the solution was stirred at room temperature for 2 hours. The mixture was then concentrated under vacuum, and the residue was triturated with diethyl ether (1 L) to crystallise the triphenylphosphine oxide formed. The suspension was filtered, and the filtrate was concentrated under vacuum. The same procedure was repeated twice using diethyl ether (2 x 500 mL), then petroleum spirit (500 mL). After the final crystallisation, the crude yellow oil was purified by filtration on a silica pad, eluting with 1:9 AcOEt:Petrol, to give 92.6 g (58 %) of a light yellow oil. IR (neat) 1370 (s), 1253 (m), 1176 (s), 860 (s), 840 (s), 692 (m), 535 (m); ^{1}H-NMR (500 MHz, $CDCl_3$, 298 K) δ 3.60-3.56 (m, 2 H, $C\underline{H}_2$), 1.30-1.26 (m, 2 H, $C\underline{H}_2$), 0.08 (s, 9 H, TMS); ^{13}C-NMR (125 MHz, $CDCl_3$, 298 K) δ 63.4 ($\underline{C}H_2$), 11.9 ($\underline{C}H_2$), -2.1 (TMS).

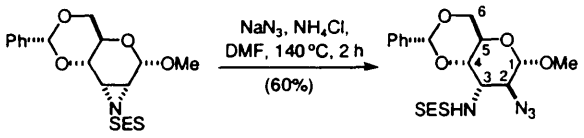
Methyl 4,6-*O*-benzylidene-2,3-dideoxy-2,3-[*N*-(2-trimethylsilylethylsulfonamido)]epimino-α-D-allo-pyranoside (250)



SESCl (5.00 g, 24.9 mmol) was added dropwise to a solution of the Hough-Richardson aziridine **234** (5.50 g, 20.8 mmol) and triethylamine (26.8 ml, 191 mmol) in freshly distilled THF (80 ml). After 24 hours stirring at room temperature under nitrogen, water was added (50 ml), and the product was extracted with diethyl ether (3 x 30 ml). The combined organic layer was washed with water (50 ml), brine (20 mL) and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the product was recrystallised in hot isopropanol to give **250** (5.5 g) as a white solid. A further crop (0.5 g, overall yield 67%) was obtained after concentration of the mother liquor, and purification of the residue by SiO_2 flash chromatography

(Et_2O/Petrol 1:1). $[\alpha]_D$ +77.3 ° (*c* 0.4, CH_3Cl_3); IR (KBr) 2955 (s), 2920 (m), 1677 (w), 1455 (m), 1395 (s), 1325 (s), 1287 (m), 1255 (s), 1224 (s), 1144 (s), 1108 (s), 1067 (s), 981 (s), 913 (s), 836 (s), 756 (s), 699 (s) 672 (m), 630 (w), 597 (m), 563 (w), 540 (w), 515 (w); ^{1}H-NMR (500 MHz, $CDCl_3$, 298 K) δ 7.45-7.43 (m, 2 H, arom.), 7.33-7.32 (m, 3H, arom.), 5.57 (s, 1 H, PhC<u>H</u>-), 4.94 (d, *J* = 4.1 Hz, 1 H, H1), 4.21 (dd, *J* = 10.3, 5.0 Hz, 1 H, H6), 4.03 (ddd, *J* = 10.0, 9.5, 5.0 Hz, 1 H, H5), 3.89 (dd, *J* = 9.1, 2.6 Hz, 1 H, H4), 3.66 (dd, *J* = 10.3, 10.3 Hz, 1 H, H6), 3.44 (s, 3 H, -OC<u>H</u>$_3$), 3.36 (dd, *J* = 7.2, 4.1 Hz, 1 H, H2), 3.24 (dd, *J* = 7.2, 2.5 Hz, 1 H, H3), 3.19 (ddd, *J* = 14.1, 14.1, 4.3 Hz, 1 H, SES), 3.11 (ddd, *J* = 14.1, 14.1, 4.2 Hz, 1 H, SES), 1.22 (ddd, *J* = 13.9, 13.8, 4.4 Hz, 1 H, SES), 1.11 (ddd, *J* = 13.9, 13.8, 4.3 Hz, 1 H, SES), -0.07 (s, 9 H, TMS) ; ^{13}C-NMR (125 MHz, $CDCl_3$, 298 K) δ 137.1 (arom.), 129.2 (arom.), 128.3 (arom.), 126.2 (arom.), 102.5 (Ph<u>C</u>H-), 94.0 (C1), 75.2 (C4), 68.9 (C6), 60.5 (C5), 56.0 (-O<u>C</u>H$_3$), 49.2 (SES), 38.9 (C3), 38.6 (C2), 9.6 (SES), -2.3 (TMS); HRMS Calcd for $C_{19}H_{30}NO_6SSi$ $(M+H)^+$: *m/z* 428.15630. Found: *m/z* 428.15586.

Methyl 2-azido-4,6-*O*-benzylidene-2,3-dideoxy-3-(2-trimethylsilyl-ethylsulfonamido)-α-D-altro-pyranoside (251)

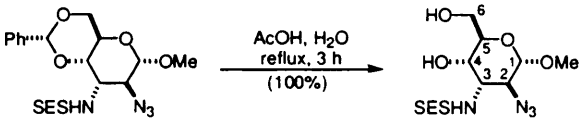


250 **251**

Sodium azide (3.10 g , 47.4 mmol) and ammonium chloride (1.00 g, 19.0 mmol) were suspended in solution of the *N*-protected aziridine **250** (5.07 g, 11.9 mmol) in DMF (65 ml), and the mixture was refluxed for 2 hours. After cooling to room temperature, water (100 ml) was added and the product was extracted with diethyl ether (3x 20 ml). The combined organic layer was washed with water (10 mL), brine (5 mL), and dried ($MgSO_4$). After evaporation of the solvent *in vacuo*, the residue was purified by recrystallisation in hot isopropanol to give **251** (3.08 g, 55%) as a white solid. The mother liquor was concentrated, and after SiO_2 flash chromatography (Et_2O/Petrol 1:1), another crop of the product (0.280 g, overall yield 60 %) was obtained. $[\alpha]_D$ +60.2 ° (*c* 0.21, CH_3Cl_3); IR (KBr) 3359 (m), 2950 (m) 2878 (m), 2187 (w), 2105 (s), 1436 (m), 1332 (s), 1259 (s), 1142 (s), 1112 (s), 1078 (m), 1046 (s), 989 (m), 945 (m), 844 (m), 768 (m), 701 (m), 540 (w), 508 (w); ^{1}H-NMR (500 MHz, $CDCl_3$, 298 K) δ 7.43-7.40 (m, 2 H, arom.), 7.33-7.30 (m, 3 H, arom.), 5.60 (s, 1 H, PhC<u>H</u>-), 5.38 (d, *J* = 9.3 Hz, 1 H, -N<u>H</u>SES), 4.70 (s, 1 H, H1), 4.31 (m, 1 H, H6), 4.03 (ddd, *J* = 9.3, 2.8, 2.7 Hz, 1 H, H3), 3.98 (dd, *J* = 2.8, 1.1 Hz, 1 H, H2), 3.93-3.81 (m, 2 H, H4 + H5), 3.79-3.76 (m, 1 H, H6), 3.44 (s, 3 H, -OC<u>H</u>$_3$), 2.88-2.83 (m, 2 H, SES), 0.94-0.89 (m, 2 H, SES), -0.25 (s, 9 H, TMS) ; ^{13}C-NMR (125 MHz, $CDCl_3$, 298 K) δ 137.0 (arom.), 129.2 (arom.), 128.4 (arom.), 126.0 (arom.), 102.4 (Ph<u>C</u>H-), 99.4 (C1),

73.8 (C4), 69.0 (C6), 62.3 (C2), 59.4(C5), 56.0 (-O<u>C</u>H$_3$), 51.8 (C3), 50.4 (SES), 10.0 (SES), -2.3 (TMS); HRMS Calcd for $C_{19}H_{31}N_4O_6SSi$ $(M+H)^+$: *m/z* 471.17335. Found: *m/z* 471.17315.

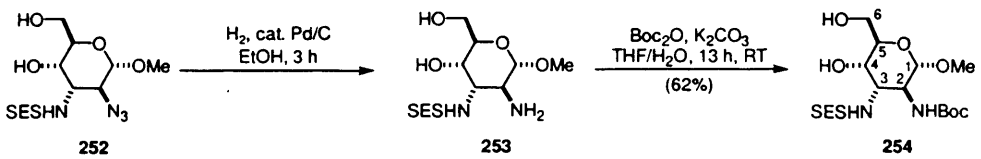
Methyl 2-azido-2,3-dideoxy-3-trimethylsilylethylsulfonamido-α-D-altropyranoside (252)



251 **252**

Benzylidene acetal **251** (1.33 g, 2.83 mmol) was refluxed for 3 hours in a mixture of water (6 ml), acetic acid (25 ml) and methanol (6 ml). After cooling to room temperature, the solvents were removed by distillation *in vacuo*. The residue was purified by SiO_2 flash chromatography (AcOEt/Petrol 6:4) to give **252** (1.05 g, 100%) as a thick oil. $[\alpha]_D$ +32.8 ° (*c* 0.45, CH_3Cl_3); IR (neat) 3340 (s), 2953 (s), 2111 (s), 1445 (m), 1323 (s), 1257 (s), 1141 (s), 983 (m), 953 (m), 858 (s), 785 (m), 760 (m), 699 (s), 539 (m), 503 (m); ^{1}H-NMR (500 MHz, $CDCl_3$, 298 K) δ 5.64 (d, *J* = 9.5 Hz, 1H, -N<u>H</u>Ses), 4.69 (s, 1 H, H1), 3.97 (m., 1H, H4), 3.85 (m, 2 H, H6), 3.77 (m, 2 H, H2 and H3), 3.69 (m, 1 H, H5), 3.05 (m, 2H, SES), 2.85 (br s, 1 H, -CH$_2$O<u>H</u>), 2.39 (s, 1 H, -CHO<u>H</u>), 1.06 (m, 2H, SES), 0.05 (s, 9H, TMS); ^{13}C-NMR (125 MHz, $CDCl_3$ 298 K) δ 99.6 (C1), 70.3 (C5), 63.9 (C4), 62.2 (C6), 61.5 (C2), 55.8 (-O<u>C</u>H$_3$), 54.3 (C3), 50.0 (SES), 10.4 (SES), -2.05 (TMS); HRMS Calcd for $C_{12}H_{27}N_4O_6SSi$ $(M+H)^+$: *m/z* 383.14205. Found: *m/z* 383.14392.

Methyl 2-butoxycarbonylamino-2,3-dideoxy-3-trimethylsilylethylsulfonamido-α-D-altropyranoside (254)

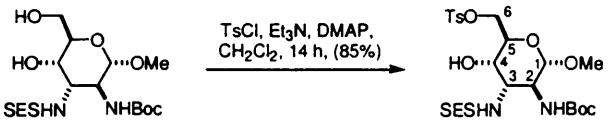


252 **253** **254**

Azide **252** (1.22 g, 3.19 mmol) was vigorously stirred in the presence of 10% wet Pd/C (1.2 g, 0.319 mmol) in absolute ethanol (40 ml) under a hydrogen atmosphere (1 atm.). After 2 hours stirring, the suspension was filtered on a pad of celite, and the solvent was evaporated *in vacuo*. The white crude solid thus obtained was dissolved in 3:1 THF/water (40 ml). Di-*tert*-butyl dicarbonate (1.00 g, 4.79 mmol) was added, followed by K_2CO_3 (0.8 g, 6.28 mmol). The mixture

was vigorously stirred at room temperature for 13 h. The mixture was diluted with AcOEt (100 mL), and the layers were separated. The organic layer was washed with brine (20 mL), and dried ($MgSO_4$). After removal of the solvent under vacuum, the residue was purified by SiO_2 flash chromatography (AcOEt/Petrol 6:4) to yield carbamate **254** (0.910 g, 62%) as a white solid. $[\alpha]_D$ −18.6 ° (*c* 0.5 CH_3Cl_3); IR (KBr) 3360 (m), 2958 (m), 1708 (s), 1522 (m), 1370 (m), 1324 (s), 1253 (s), 1144 (s), 1094 (m), 1049 (s), 978 (w), 860 (m), 741 (s), 699 (w), 500 (w); ^{1}H-NMR (500 MHz, $CDCl_3$, 298 K) δ 5.75 (d, *J* = 8.8 Hz, 1 H, -NHSes), 5.18 (d, *J* = 7.8 Hz, 1 H, -NHBoc), 4.95 (s, 1 H, H1), 4.11 (m, 3 H, H2, H4 and H6), 3.90 (br s, 2 H, H3 and H6), 3.62 (m, 1 H, H5), 3.41 (s, 3 H, -OCH_3), 3.21 (m, 2 H, -CH_2SO_2), 3.06 (d, *J* = 7.1 Hz, 1 H, -CH_2OH), 2.52 (br s, 1 H, -CHOH), 1.43 (s, 9 H, Boc), 1.15 (td, *J* = 13.5, 3.4 Hz, 1 H, SES); 1.05 (td, *J* = 13.5, 4.6 Hz, 2 H, SES), 0.09 (s, 9 H, TMS); ^{13}C-NMR (125 MHz, $CDCl_3$, 298 K) δ 154.5 (C=O), 100.0 (C1), 80.5 (Boc), 68.8 (C5), 62.5 (C4), 62.0 (C6), 55.5 (-OCH_3), 54.1 (C3), 52.6 (C2), 48.6 (SES), 28.2 (Boc), 10.5 (SES), -2.1 (TMS); HRMS Calcd for $C_{17}H_{37}N_2O_8SSi$ $(M+H)^+$: *m/z* 457.20398. Found: *m/z* 457.20456.

Methyl 2-butoxycarbonylamino-2,3-dideoxy-6-*p*-toluenesulfonyl-3-trimethylsilyl-ethylsulfonamido-α-D-altropyranoside (255)

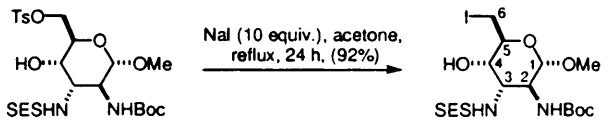


254 **255**

To the solution of diol **254** (416 mg, 0.911 mmol) in freshly distilled CH_2Cl_2 (16 ml) under nitrogen was added anhydrous Et_3N (1.90 ml, 13.7 mmol), and the solution was cooled to 0°C. Recrystallised *p*-TsCl (209 mg, 1.09 mmol) and DMAP (11.0 mg, 0.0911 mmol) where added to the mixture under stirring. The cold bath was removed and the solution was stirred for 14 hours at room temperature. The solution was washed with sat. aq. NH_4Cl (5 mL), water (5 mL), brine and dried ($MgSO_4$). After evaporation of the solvent, the residue was purified by SiO_2 flash chromatography (AcOEt/Petrol 4:6) to give the title compound (455 mg, 85 %) as a white solid. $[\alpha]_D$ +22.6 ° (*c* 0.5, CH_3Cl_3); IR (KBr) 3372 (s), 2958 (m), 1710 (s), 1512 (m), 1367 (s), 1253 (m), 1177 (s), 1143 (s), 1098 (m), 1054 (m), 965 (m), 841 (m), 667 (w), 554 (w); ^{1}H-NMR (500 MHz, $CDCl_3$, 298 K) δ 7.79 (d, *J* = 8.2 Hz, 2 H, arom.), 7.33 (d, *J* = 8.0 Hz, 2 H, arom.), 5.63 (d, *J* = 9.1 Hz, 1 H, -NHSES), 4.84 (d, *J* = 7.8 Hz, 1 H, -NHBoc), 4.55 (s, 1 H, H1), 4.36 (d, *J* = 10.6 Hz, 1 H, H6), 4.21 (dd, *J* = 10.8, 5.5 Hz, 1 H, H6), 3.85 (d, *J* = 7.5 Hz, 1 H, H2), 3.75-3.72 (m, 1 H, H3), 3.68 (m, 1 H, H5), 3.63 (dd, *J* = 10.0, 3.9 Hz, 1 H, H4), 3.36 (s, 3 H, -OCH_3), 3.16 (m, 2 H, SES), 2.43 (s, 3 H, PhCH_3), 1.41 (s, 9 H, Boc), 1.12 (td, *J* = 13.6, 3.6 Hz, 1 H, SES), 1.00 (td, *J* = 13.8, 4.4 Hz, 1 H, SES), 0.06 (s, 9 H, SES) ; ^{13}C-NMR (125 MHz, $CDCl_3$, 298

K) δ 154.4 (C=0), 145.0 (arom.), 132.8 (arom.), 129.9 (arom.), 128.0 (arom.), 99.8 (C1), 80.8 (Boc), 69.2 (C6), 67.2 (C5), 61.9 (C4), 55.7 (-O<u>C</u>H$_3$), 53.9 (C3), 52.5 (C2), 48.6 (SES), 28.2 (Boc), 21.7 (Ph<u>C</u>H$_3$), 10.5 (SES), -2.1 (TMS); HRMS Calcd for $C_{24}H_{43}N_2O_{10}S_2Si$ $(M+H)^+$: *m/z* 611.21283. Found: *m/z* 611.21169.

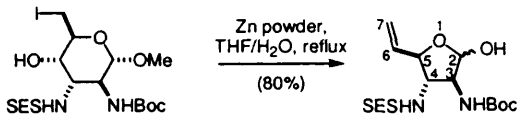
Methyl 2-butoxycarbonylamino-2,3-dideoxy-6-iodo-3-trimethylsilylethylsulfonamido-α-D-altropyranoside (232)



255 **232**

NaI (1.10 g, 7.37 mmol) was dissolved into a solution of tosylate **255** (450 mg, 0.737 mmol) in acetone (20 mL), and the mixture was refluxed for 24 hours. The solvent was evaporated under reduced pressure, and the residue was taken up in ethyl acetate (50 mL). The solution was washed with a sat. aq. $Na_2S_2O_3$ (5 mL) water (5 mL) , brine (2 mL), and dried ($MgSO_4$). After concentration of the solution, the residual solid was purified by SiO_2 flash chromatography (AcOEt/Petrol 2:8) to give **232** (383 mg, 92%) as a yellow solid, unstable to light exposure. $[\alpha]_D$ –2.2 ° (*c* 0.5, CH_3Cl_3); IR (KBr) 3425 (s), 1708 (s), 1324 (m), 1143 (s); ^{1}H-NMR (500 MHz, $CDCl_3$, 298 K) δ 5.69 (d, *J* = 9.2 Hz, 1 H N<u>H</u>SES), 4.80 (d, *J* = 7.8 Hz, 1 H, N<u>H</u>Boc), 4.63 (s, 1 H, H1), 3.89 (d, *J* = 7.8 Hz, 1 H, H2), 3.75 (m, 1 H, H3), 3.65 (dd, *J* = 10.6, 1.9 Hz, 1 H, H6), 3.53 (dd, *J* = 9.8, 4.1 Hz, 1 H, H4), 3.48 (m, 1 H, H5) superimposed upon 3.46 (s, 3 H, -OC<u>H</u>$_3$), 3.28 (dd, *J* = 10.7, 7.6 Hz, 1 H, H6), 3.24-3.11 (m, 2 H, SES), 1.41 (s, 9 H, Boc), 1.11 (m, 1 H, SES), 1.00 (m, 1 H, SES), 0.05 (s, 9 H), TMS) ; ^{13}C-NMR (125 MHz, $CDCl_3$, 298 K) δ 154.4 (C=0), 100.1 (C1), 80.8 (Boc), 68.8 (C5), 66.5 (C4), 55.9 (-O<u>C</u>H$_3$), 54.1 (C3), 52.8 (C2), 42.0 (SES), 28.2 (Boc), 10.6 (SES), 6.6 (C6), -2.0 (TMS); HRMS Calcd for $C_{17}H_{36}IN_2O_7SSi$ $(M+H)^+$: *m/z* 567.10572. Found: *m/z* 567.10483.

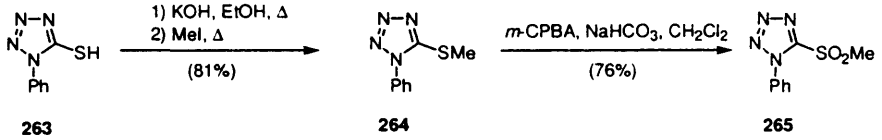
Hemiacetal 231



232 231

Zinc powder (Aldrich 20,998-8, 3.70 g, 56.5 mmol) was suspended in a solution of iodide **232** (3.67 g, 5.39 mmol) in a 9:1 mixture of THF/water (30 ml), and the mixture was refluxed. After 2 h, the mixture was cooled down to room temperature and filtered on a Celite pad. After concentration under vacuum, the residue was taken in AcOEt (100 mL) and water (20 mL). The layers were separated, and the organic layer was washed with water (20 mL), brine (10 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was purified by SiO_2 flash chromatography (AcOEt/Petrol 4:6) to give **231** (180 mg, 80%) as a white foam. $[\alpha]_D$ +2.8 ° (*c* 1, CH_3Cl_3); IR (neat) 3349 (br s), 2956 (s), 1694 (s), 1517 (s), 1455 (w), 1428 (w), 1391 (w), 1368 (m), 1322 (s), 1251 (s), 1170 (s), 1139 (s), 1009 (m), 936 (w), 895 (w), 862 (s), 759 (s), 700 (m) ; ^{1}H-NMR (500 MHz, toluene-d_8, 373 K) δ 5.89 (ddd, *J* = 17.1, 10.4, 6.8 Hz, 1 H, H6β), 5.80 (ddd, *J* = 16.3, 10.6, 5.7 Hz, 1 H, H6α), 5.27 (ddd, J = 17.2, 1.5, 1.5 Hz, 1 H, H7α), 5.21 (ddd, *J* = 17.1, 1.6, 1.2 Hz, 1 H, H7β), 5.07 (br d, *J* = 7.8 Hz, 1 H, NHBoc β), 5.00 (ddd, *J* = 10.4, 1.6, 1.1 Hz, 1 H, H7β), 4.96 (ddd, *J* = 10.4, 1.5, 1.5 Hz, 1 H, H7α), 4.95 (m, 2 H, H2), 4.86 (br d, *J* = 7.3 Hz, 1 H, NHSES β), 4.52 (br d, *J* = 6.7 Hz, 1 H, NHBoc α), 4.38 (dddd, *J* = 5.7, 5.7, 1.4, 1.4 Hz, 1 H, H5α), 3.94 (dddd, *J* = 6.9, 6.9, 1.0, 1.0 Hz, 1 H, H5β), 3.91 (ddd, *J* = 9.9, 7.9, 4.7 Hz, 1 H, H3β), 3.84 (ddd, *J* = 7.4, 4.4, 2.0 Hz, 1 H, H3α), 3.67 (ddd, *J* = 9.8, 8.0, 8.0 Hz, 1 H, H4β), 3.03 (br s, 1 H, OH α), 2.88 (m, 2 H, SES α), 2.77 (m, 2 H, SES β), 2.58 (br s, 1 H, OH β), 1.36 (s, 9 H, Boc β), 1.32 (s, 9 H, Boc α), 0.97 (m, 2 H, SES α + β), -0.12 (s, 9 H, SES α), -0.14 (s, 9 H, SES β) ; ^{13}C-NMR (125 MHz, toluene-d_8, 373 K) δ 156.8 (C=O), 156.0 (C=O), 138.6 C6β), 137.0 (C6α), 117.4 (C6β), 116.7 (C7α), 101.7 (C2α), 95.2 (C2β), 84.6 (C5α), 83.1 (C5β), 80.5 (Boc), 64.8 –C3α), 64.1 (C4α), 62.4 (C4β), 59.8 (C3β), 51.3 (SES β), 50.9 (SES α), 28.7 (Boc), 11.3 (SES), -1.9 (TMS); HRMS Calcd for $C_{16}H_{33}N_2O_6SSi$ $(M+H)^+$: *m/z* 409.18285. Found: *m/z* 409.18359.

Sulfone 265

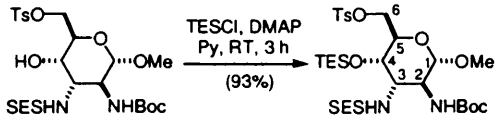


263 **264** **265**

5-Methylsulfanyl-1-phenyl-1*H*-tetrazole (264). To a solution of potassium hydroxide (17.3 g, 0.309 mol) in absolute ethanol (560 mL) was added 1-phenyl-1*H*-tetrazole-5-thiol **263** (50 g, 0.281 mol) and the mixture was refluxed. After 2 hour, the reaction mixture was cooled down to room temperature and iodomethane (19.2 mL, 0.309 mol) was slowly added. The mixture was refluxed for another 2 hours. After cooling to room temperature, water (1 L) was added, and the solution was extracted with diethyl ether (3 x 500 mL). The combined organic layer was washed with saturated aq. $NaHCO_3$ (200 mL), brine (200 mL), and dried ($MgSO_4$). The solvent was removed under vacuum to yield 43.6 g (81 %) of a white solid. M.p. 76°C; IR (KBr) 1593 (m), 1501 (s), 1465 (m), 1418 (s), 1385 (s), 1313 (s), 1278 (s), 1248 (s), 1166 (w), 1095 (s), 1078 (m), 1042 (w), 1012 (m), 979 (s), 788 (s), 693 (s), 554 (m); ^{1}H-NMR (400 MHz, $CDCl_3$, 298 K) δ 7.56-7.52 (m, 5 H, Ph), 2.81 (s, 3 H, Me); ^{13}C-NMR (100 MHz, $CDCl_3$ 298 K) δ 154.9, 133.6, 130.1, 129.8, 123.7, 15.4; HRMS Calcd for $C_8H_9N_4S$ $(M+H)^+$: *m/z* 193.05478. Found: *m/z* 193.05519.

5-Methanesulfonyl-1-phenyl-1*H*-tetrazole (265). 3-Chloroperoxybenzoic acid (77 % in water, 122.5 g, 0.546 mol) was added portionwise to a suspension of the above thioether (42 g, 0.219 mol) and $NaHCO_3$ (92 g, 1.1 mol) in dichloromethane under mechanical stirring. The mixture was vigorously stirred for 10 hours. Saturated solutions of aq. $NaHCO_3$ (1 L) and aq. $Na_2S_2O_3$ (500 mL) were added, and the stirring was continued for another 1 hour until the solution became clear. The layers were separated. The aqueous layer was further extracted with dichloromethane (2 x 200 mL). The combined organic layer was washed with water (300 mL), brine (150 mL), and dried ($MgSO_4$). The solvent was removed under vacuum to yield an oil which crystallised upon addition of diethyl ether. The pale yellow solid thus obtained was recrystallised in hot ether to afford 37.1 g (76 %) of a bright white solid. M.p. 86°C; IR (KBr) 1593 (m), 1497 (m), 1458 (w), 1405 (w), 1336 (s), 1157 (s), 1107 (w), 1073 (w), 1054 (w), 1018 (w), 960 (m), 768 (s), 689 (s), 570 (m), 533 (s), 500 (s); ^{1}H-NMR (400 MHz, $CDCl_3$, 298 K) δ 7.69-7.67 (m, 2 H, Ph), 7.61-7.58 (m, 3 H, Ph), 3.61 (s, 3 H, Me); ^{13}C-NMR (100 MHz, $CDCl_3$ 298 K) δ 154.0, 132.9, 130.1, 131.5, 124.9, 43.8; HRMS Calcd for $C_8H_9N_4O_2S$ $(M+H)^+$: *m/z* 225.04461. Found: *m/z* 225.04403.

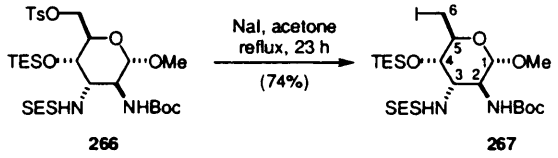
Methyl 2,3-dideoxy-2-methoxycarbonylamino-6-*p*-toluenesulfonyl-4-triethylsilyl-3-trimethylsilyl-ethylsulfonamido-α-D-altropyranoside (266)



255 266

To a solution of alcohol **255** (500 mg, 0.819 mmol) in dry pyridine (3 mL) under nitrogen was added chlorotriethylsilane (200 µL, 1.23 mmol), followed by DMAP (15 mg, 0.123 mmol). After 3 h stirring at room temperature, the solvent was evaportated by distillation under reduced pressure. The residue was taken up in AcOEt (50 mL), and the solution was extensively washed with 0.5N aq. HCl (5 x 10 mL), sat. aq. $NaHCO_3$ (10 mL), brine (5 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was purified by SiO_2 flash chromatography (AcOEt/Petrol 3:7) to give **266** (555 mg, 93%) as a white solid. M.p. 101 °C; $[\alpha]_D$ +20.3 ° (*c* 0.37, CH_3Cl_3); IR (neat) 2957 (s), 1709 (s), 1599 (w), 1517 (w), 1458 (w), 1368 (s), 1250 (m), 1178 (s), 1145 (s), 1095 (m), 1053 (m), 1021 (w), 968 (w), 942 (w), 862 (m), 739 (m), 698 (w), 665 (m), 554 (s) ; ^{1}H-NMR (500 MHz, $CDCl_3$, 298 K) δ 7.79 (d, *J* = 8.3 Hz, 2 H, arom.), 7.39 (d, *J* = 8.0 Hz, 2 H, arom.), 5.36 (d, *J* = 8.3 Hz, 1 H, NHSES), 4.68 (d, *J* = 7.4 Hz, 1 H, NHBoc), 4.48 (s, 1 H, H1), 4.29 (d, *J* = 10.7 Hz, 1 H, H4), 4.12 (m, 1 H, H5), 3.82 (d, *J* = 6.9 Hz, 1 H, H2), 3.76-3.72 (m, 3 H, H2 + H6), 3.32 (s, 3 H, -OC$\underline{H}_3$), 3.14 (t, *J* = 13.4 Hz, 1 H, SES), 3.05 (t, *J* = 13.1 Hz, 1 H, SES), 2.44 (s, 3 H, PhC$\underline{H}_3$), 1.42 (s, 9 H, Boc), 1.23 (m, 2 H, SES), 0.91 (m, 9 H, TES), 0.58 (m, 6 H, TES), 0.03 (s, 9 H, TMS) ; ^{13}C-NMR (125 MHz, $CDCl_3$, 298 K) δ 154.3 (C=O), 144.9 (arom.), 133.0 (arom.), 129.8 (arom.), 128.0 (arom.), 100.0 (C1), 80.5 (Boc), 69.2 (C4), 67.0 (C5), 63.7 (C6), 55.6 (-O$\underline{C}H_3$), 54.5 (C3), 52.7 (C2), 49.8 (SES), 28.2 (Boc), 21.6 (Ph$\underline{C}H_3$), 10.4 (SES), 6.8 (TES), 4.5 (TES), -2.0 (TMS); HRMS Calcd for $C_{30}H_{56}N_2O_{10}S_2Si_2Na$ $(M+Na)^+$: *m/z* 747.28125. Found: *m/z* 747.28164.

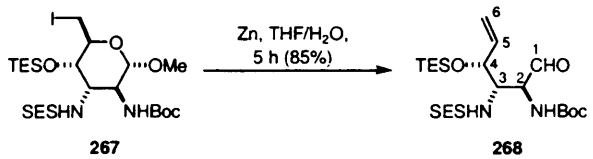
Methyl 2,3-dideoxy-6-iodo-2-methoxycarbonylamino-4-triethylsilyl-3-trimethylsilyl-ethylsulfonamido-α-D-altropyranoside (267)



266 267

Sodium iodide (11.1 g, 74.3 g) was added to a solution of tosylate **266** (5.39 g, 7.43 mmol) in acetone (300 mL), and the mixture was refluxed overnight. After 23 h, the mixture was cooled down to room temperature, and filtered. The clear yellow filtrate was concentrated *in vacuo*. The residue was taken up in AcOEt (200 mL), and the resulting solution was washed with water (30 mL), brine (20 mL), and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was purified by SiO_2 flash chromatography (AcOEt/Petrol 15:85) to give **267** (3.75 g, 74%) as a colourless oil. $[\alpha]_D$ +15.4 ° (*c* 0.5, CH_3Cl_3); IR (KBr) 2954 (s), 1685 (s), 1474 (m), 1370 (m), 1341 (w), 1319 (s), 1250 (m), 1176 (m), 1148 (s), 1106 (m), 1088 (m), 1050 (m), 1027 (m), 966 (m), 895 (w), 859 (m), 831 (m), 803 (w), 777 (w), 739 (w), 739 (m), 694 (w) ; ^{1}H-NMR (500 MHz, $CDCl_3$, 298 K) δ 5.42 (d, *J* = 9.1 Hz, 1 H, NHSES), 4.73 (d, *J* = 7.4 Hz, 1 H, NHBoc), 4.59 (s, 1 H, H1), 3.87 (d, *J* = 6.3 Hz, 1 H, H2), 3.76 (m, 1 H, H3), 3.65 (m, 1 H, H4), 3.64-3.49 (m, 2 H, H6 + H5), 3.44 (s, 3 H, -OCH_3), 3.20 (m, 1 H, H6), 3.16 (m, 1 H, SES), 3.07 (m, 1 H, SES), 1.41 (s, 9 H, Boc), 1.07 (m, 2 H, SES), 0.96 (t, *J* = 8.0 Hz, 9 H, TES), 0.72-0.66 (m, 5 H, TES), 0.04 (s, 9 H, TMS) ; ^{13}C-NMR (125 MHz, $CDCl_3$, 298 K) δ 154.3 (C=O), 100.4 (C1), 80.5 (Boc), 68.3 (C5), 68.1 (C4), 55.9 (-OCH_3), 54.7 (C3), 52.9 (C2), 49.9 (SES), 28.2 (Boc), 10.5 (SES), 7.5 (C6), 6.9 (TES), 4.9 (TES), -2.0 (TMS); HRMS Calcd for $C_{23}H_{49}IN_2O_7SSi_2Na$ $(M+Na)^+$: *m/z* 703.17413. Found: *m/z* 703.17290.

Aldehyde 268

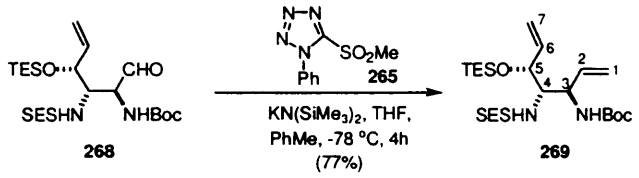


267 268

Zinc powder (Aldrich 20,998-8, 7.05 g, 108 mmol) was suspended in a solution of iodide **267** (3.67 g, 5.39 mmol) in a 4:1 THF/water (110 ml), and the mixture was refluxed. After 5 h, the mixture was cooled down to room temperature and filtered on a Celite pad. The solution was diluted with AcOEt (500 mL), and the layer were separated. The aqueous layer was further

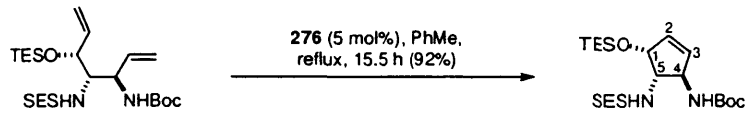
extracted with AcOEt (2 x 20 mL). The combined organic layer was washed with brine (50 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was purified by SiO_2 flash chromatography (AcOEt/Petrol 15:85) to give aldehyde **268** (2.2 g, 85%) as a colourless oil. IR (neat) 3357 (m), 2956 (m), 1385 (m), 1094 (s), 767 (s); ^{1}H-NMR (500 MHz, $CDCl_3$, 298 K) δ 9.60 (s, 1 H, H1), 5.83 (ddd, *J* = 17.1, 10.4, 6.5 Hz, 1 H, H5), 5.76 (d, *J* = 6.2 Hz, 1 H, NHBoc), 5.37 (d, *J* = 17.2 Hz, 1 H, H6), 5.30 (d, *J* = 10.5 Hz, 1 H, H6), 4.73 (d, *J* = 7.8 Hz, 1 H, NHSES), 4.42 (dd, *J* = 4.9, 6.1 Hz, 1 H, H4), 4.26 (br s, 1 H, H2), 3.87 (ddd, *J* = 7.8, 4.5, 3.4 Hz, 1 H, H3), 2.97-2.93 (m, 2 H, SES), 1.46 (s, 9 H, Boc), 0.96 (t, *J* = 7.9 Hz, 6 H, TES), 0.93 (t, *J* = 7.9 Hz, 3 H, TES), 0.65 (q, *J* = 7.8 Hz, 4 H, TES), 0.52 (q, *J* = 7.8 Hz, 2 H, TES), 0.07 (s, 9 H, TMS) ; ^{13}C-NMR (125 MHz, $CDCl_3$, 298 K) δ 200.2 (C1), 156.0 (C=O), 136.3 (C5), 118.6 (C6), 80.5 (Boc), 75.9 (C4), 59.8 (C2), 57.5 (C3), 49.0 (SES), 28.2 (Boc), 10.2 (SES), 6.8 (TES), 6.7 (TES), -2.0 (TMS).

Diene 269



To a solution of sulfone **265** (1.14 g, 5.10 mmol) and aldehyde **268** (2.22 g, 4.25 mmol) in freshly distilled THF (110 mL) at –78°C under N_2 was added KHMDS (0.5 M soln. in toluene, 10.2 mL, 15.7 mmol) in a dropwise manner. After the end of the addition, the mixture was stirred at -78°C for 4 h. Water (40 mL) was added to quench the reaction, and the mixture was allowed to warm to room temperature under vigorous stirring. The product was extracted with AcOEt (3 x 100 mL). The combined organic layer was washed with brine (50 mL), and dried ($MgSO_4$) After concentration under vacuum, the residue was purified by SiO_2 flash chromatography (AcOEt/Petrol 1:9) to afford diene **269** (1.70 g, 77%) as an oil. $[\alpha]_D$ +22.6 ° (*c* 1, CH_3Cl_3); IR (neat) 3356 (br s), 2956 (s), 1691 (s), 1457 (m), 1320 (m), 1250 (m), 1169 (s), 911 (m), 899 (w), 734 (s); ^{1}H-NMR (500 MHz, $CDCl_3$, 298 K) δ 5.84 (ddd, *J* = 17.0, 10.4, 6.4 Hz, 1 H, H 6), 5.77 (ddd, *J* = 17.2, 10.3, 7.0 Hz, 1 H, H2), 5.29 (d, *J* = 17.3 Hz, 1 H, H7), 5.28 (d, *J* = 10.3 Hz, 1 H, H7), 5.25 (d, *J* = 17.6 Hz, 1 H, H1), 5.22 (d, *J* = 10.3 Hz, 1 H, H1) superimposed upon 5.20 (m, 1 H, NHBoc), 4.60 (d, *J* = 8.9 Hz, 1 H, NHSES), 4.27 (m, 1 H, H5), 4.14 (m, *J* = 7.3 Hz, 1 H, H3), 3.46 (dd, *J* = 7.3, 3.9 Hz, 1 H, H4), 2.95 (m, 2 H, SES), 1.41 (s, 9 H), Boc), 1.04-1.00 (m, 2 H, SES), 0.92 (t, 9 H, TES), 0.57 (q, 6 H, TES), 0.02 (s, 9 H, TMS) ; ^{13}C-NMR (125 MHz, $CDCl_3$, 298 K) δ 156.0 (C=0), 136.1 (C6), 118.5 (C7), 117.9 (C1), 79.9 (BOC), 74.1 (C5), 62.3 (C4), 54.4 (C3), 50.5 (SES), 28.3 (BOC), 10.4 (SES), 6.8 (TES), 4.8 (TES), -1.9 (TMS); HRMS Calcd for $C_{23}H_{49}N_2O_5SSi_2$ $(M+H)^+$: *m/z* 521.29005. Found: *m/z* 521.29048.

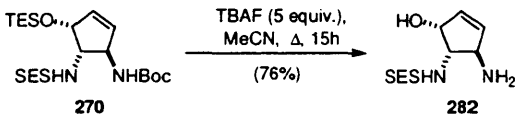
Preparation of Cyclopentene 270



269 **270**

To a degassed solution of diene **269** (1.50 g, 2.88 mmol) in freshly distilled toluene (150 mL) under nitrogen was added the Grubbs-Hoveyda catalyst **276** (90 mg, 0.144 mmol), and the mixture was refluxed. After 15.5 h, the solvent was removed *in vacuo*, and the residue was purified by SiO_2 flash chromatography (AcOEt/Petrol 1:9) to afford the title cyclopentene **270** (1.31 g, 92%) as an oil. $[\alpha]_D$ −149.4 ° (*c* 0.5, CH_3Cl_3); IR (neat) 3358 (m), 2956 (s), 1710 (s), 1517 (m), 1418 (w), 1366 (m), 1331 (s), 1250 (s), 1171 (s), 1141 (s), 1072 (s), 1014 (m), 942 (w), 861 (w), 838 (w), 734 (m); ^{1}H-NMR (500 MHz, $CDCl_3$, 298 K) δ 5.95 (dd, *J* = 6.2, 1.5 Hz, 1 H, H3), 5.87 (ddd, *J* = 6.2, 2.4, 2.3 Hz, 1H, H2), 5.03 (d, *J* = 8.8 Hz, 1 H, -NHSES), 4.77 (br s, 1 H, NHBoc), 4.58 (ddd, *J* = 5.9, 2.4, 1.0 Hz, 1 H, H1), 4.52 (dd, *J* = 6.4, 6.2 Hz, 1 H, H4), 3.61 (ddd, *J* = 8.7, 6.4, 5.9 Hz, 1 H, H5), 2.97 (m, 2 H, SES), 1.41 (s, 9 H, Boc), 1.04 (m, 2 H, SES), 0.93 (t, *J* = 10.4 Hz, 9 H, TES), 0.59 (q, *J* = 10.6 Hz, 6 H, TES), 0.03 (s, 9 H, -TMS); ^{13}C-NMR (125 MHz, $CDCl_3$, 298 K) δ 155.7 (C=O), 137.1 (C3), 132.6 (C2), 79.8 (Boc), 73.5 (C1), 61.3 (C5), 60.7 (C4), 50.3 (SES), 28.3 (Boc), 10.6 (SES), 6.7 (TES), 5.0 (TES), -2.0 (TMS). HRMS Calcd for $C_{21}H_{44}N_2O_5SSi_2Na$ $(M+Na)^+$: *m/z* 515.24070. Found: *m/z* 515.24105.

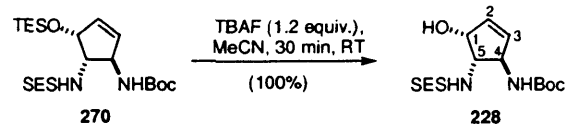
Amino-alcohol 282



270 **282**

TBAF (1M soln. in THF, 1 mL, 1 mmol) was added under nitrogen to a solution of cyclopentene **270** (100 mg, 0.203 mmol) in freshly distilled acetonitrile (3 mL). After 10 minutes, the mixture was heated at 80°C for 15 h. After cooling to room temperature, the solvent was removed by distillation under reduced pressure, and the residue was submitted to SiO_2 flash chromatography (CH_2Cl_2/MeOH 95:5) to give **282** (43 mg, 76%) as a colourless oil. IR (neat) 3363 (br s), 2956 (m), 1635 (m), 1384 (m), 1319 (m), 1251 (m), 1140 (s), 862 (m), 756 (m); Positive-CI MS *m/e* 279 (MH^+).

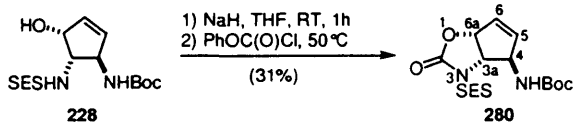
Cyclopentenol 228



270 **228**

TBAF (1 M soln. in THF, 1.5 mL, 1.5 mmol) was added under nitrogen to a solution of **270** (600 mg, 1.21 mmol) in freshly distilled acetonitrile (18 mL), and the mixture was stirred at room temperature. After 0.5 h, the solvent was removed by distillation under reduced pressure, and the residue was purified by SiO_2 flash chromatography (AcOEt/Petrol 4:6) to afford the title compound (473 mg, 100%) as a white solid. M.p. 131 °C; $[\alpha]_D$ –80.0 ° (*c* 0.065, CH_3Cl_3); IR (neat) 2961 (m), 1696 (s), 1513 (m), 1453 (w), 1392 (m), 1366 (m), 1328 (m), 1312 (m), 1251 (m), 1170 (s), 1141 (s), 1089 (w), 1061 (m), 1004 (m), 976 (w), 941 (w), 888 (m), 842 (w), 802 (w), 780 (w), 757 (w), 740 (w), 698 (w), 632 (w), 594 (w), 544 (w), 517 (w) ; ^{1}H-NMR (500 MHz, $CDCl_3$, 298 K) δ 6.03 (dt, *J* = 6.0, 2.4 Hz, 1 H, H2), 5.94 (dd, *J* = 6.1, 1.6 Hz, 1 H, H3), 5.54 (br s, 1 H, -NHSES), 4.79 (br s, 1 H, -NHBoc), 4.65 (ddd, *J* = 5.5, 2.6, 1.3 Hz, 1 H, H1), 4.62 (br s, 1 H, H4), 3.49 (ddd, *J* = 5.5 Hz, 1 H, H5), 3.01 (m, 2 H, SES), 1.81 (br s, 1 H, -OH), 1.43 (s, 9 H, Boc), 1.05 (m, 2 H, SES), 0.04 (s, 9 H, SES); ^{13}C-NMR (125 MHz, $CDCl_3$, 298 K) δ 156.1 (C=O), 136.5 (C3), 133.2 (C2), 80.2 (Boc), 73.2 (C1), 62.3 (C5), 60.2 (C4), 49.4 (SES), 28.3 (Boc), 10.4 (SES), -2.0 (TMS); HRMS Calcd for $C_{15}H_{31}N_2O_5SSi$ $(M+H)^+$: *m/z* 379.17228. Found: *m/z* 379.17164.

Cyclopentene-oxazolidinone 280

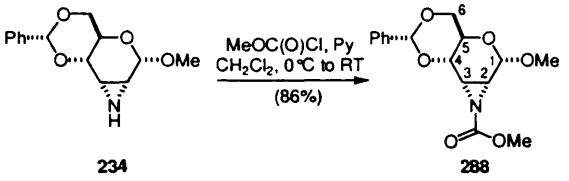


228 **280**

A solution of alcohol **228** (100 mg, 0.264 mmol) in freshly distilled THF (2 mL) was added under nitrogen to a suspension of NaH (60% dispersion in mineral oil, 13 mg, 0.317 mmol) in freshly distilled THF. After the gas evolution ceased, the mixture was stirred at room temperature. After 1 hour, phenyl chloroformate (50 µL, 0.396 mmol) was added dropwise, and the stirring was continued for 16.5 h. More NaH (6.4 mg, 0.132 mmol) was added. After 30 min., more phenyl chloroformate (20 µL, 0.158 mmol) was added to the mixture. After 30 min. stirring, the mixture was heated at 50 °C for 2.5 h. After cooling to room temperature, the solution was

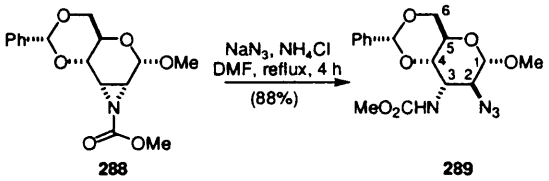
diluted with Et_2O (20 mL), and quenched with water (5 mL). The layer were separated. The organic layer was washed with sat. aq. $NaHCO_3$, brine, and dried ($MgSO_4$). After concentration *in vacuo*, the residue was purified by SiO_2 flash chromatography (AcOEt/Petrol 2:8) to afford the title compound (33 mg, 31%) as an oil. IR (KBr) 3391 (m), 2956 (m), 1779 (s), 1710 (s), 1517 (m), 1364 (s), 1251 (s), 1172 (s), 1048 (m), 862 (m), 520 (m); ^{1}H-NMR (500 MHz, $CDCl_3$, 298 K) δ 6.04-6.02 (m, 2 H, H5 and H6), 5.70 (d, *J* = 7.5 Hz, 1 H, H6a), 5.04 (br s, 1 H, NHBoc), 4.66 (d, *J* = 7.3 Hz, 1 H, H3a), 4.61 (br s, 1 H, H4), 3.50-3.43 (m, 2 H, SES), 1.39 (s, 9 H, Boc), 1.04-0.99 (m, 2 H, SES), 0.05 (s, 9 H, TMS); ^{13}C-NMR (125 MHz, $CDCl_3$, 298 K) δ 154.8, 152.2, 137.0, 129.9, 83.7, 80.3, 64.2, 63.7, 49.9, 44.9, 28.2, 9.5, -2.0.

Methyl 4,6-*O*-benzylidene-2,3-dideoxy-2,3-(*N*-methoxycarbonyl)epimino-α-D-allo-pyranoside (288)



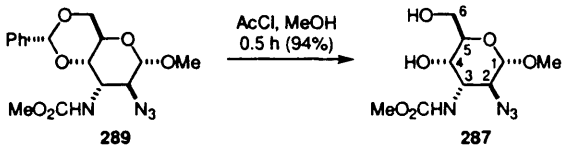
To a stirred solution of the 2,3-epimine **234** (10 g, 38 mmol) in dry CH_2Cl_2 (100 mL) and dry pyridine (9.2 mL, 114 mmol) at 0 °C was added methyl chloroformate (3.6 mL, 45.6 mmol) dropwise over 10 min. When the addition was complete, the cooling bath was removed, and the reaction mixture was allowed to warm to room temperature. After stirring for 4.5 h, water (100 mL) was added to the reaction mixture, and the resulting biphasic solution partioned in a separatory funnel. The organic layer was removed, and the aqueous fraction further extracted with CH_2Cl_2 (3 x 150 mL). The combined organic layers were washed with 0.5 M aq. HCl (2 x 100 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The title compound **288** crystallised in pure condition when the crude residue was triturated with EtOAc and petrol; the product **288** was obtained in two crops (8.2 g and 2.3 g, 86% overall). M.p. 157°C; $[\alpha]_D$ +64.3° (*c* 0.12, CH_2Cl_2); IR (KBr) 1724 (s), 1443 (s), 1416 (w), 1392 (m), 1366 (m), 1307 (s), 1220 (s), 1189 (w), 1137 (m), 1110 (s), 1065 (s), 1021 (s), 986 (s), 956 (m), 859 (w), 750 (m), 695 (m); ^{1}H-NMR (500 MHz, $CDCl_3$, 298 K) δ 7.49 (m, 2 H, arom.), 7.38-7.32 (m, 3 H, arom.), 5.56 (s, 1 H, Ph-CH-), 4.90 (d, *J* = 3.1 Hz, 1 H, H1), 4.20 (dd, *J* = 10.2, 5.1 Hz, 1 H, H6), 4.01 (m, 1 H, H5), 3.84 (dd, *J* = 9.1, 1.6 Hz, 1 H, H4), 3.73 (s, 3 H, -CO_2CH_3), 3.65 (dd, *J* = 10.3, 10.3 Hz, 1 H, H6), 3.46 (s, 3 H, -OCH_3), 3.11 (narrow m, 2 H, H2 + H3); ^{13}C-NMR (125 MHz, $CDCl_3$, 298 K) δ 162.5 (C=O), 137.2 (arom.), 128.3 (arom.), 126.4 (arom), 102.6 (PhCH-), 94.5 (C1), 76.3 (C4), 68.9 (C6), 60.1 (C5), 55.9 (-OCH_3), 54.1 (-CO_2CH_3), 39.3 (C3/C2), 36.9 (C3/C2). HRMS Calcd for $C_{16}H_{20}NO_6$ $(M+H)^+$: *m/z* 322.12905. Found: *m/z* 322.12876. Anal. for $C_{16}H_{19}NO_6$. Calcd. C: 59.81; H: 5.96; N: 4.36. Found. C: 59.83; H: 5.94; N: 4.30.

Methyl 2-azido-4,6-*O*-benzylidene-2,3-dideoxy-3-methoxycarbonylamino-α-D-altro-pyranoside (289)



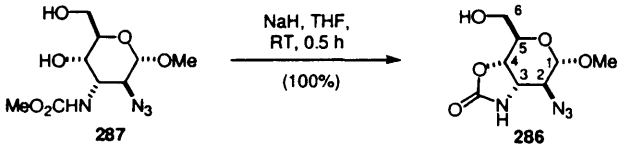
A mixture of **288** (8.2g, 25.5 mmol), NaN_3 (6.63 g, 102 mmol), and NH_4Cl (2.1 g, 40.8 mmol) in dry DMF (150 mL) were heated at reflux for 4 h, whereafter TLC analysis (4:1 EtOAc:Petrol) revealed that all of **288** had been consumed and that a single slower-moving product **289** had formed. The reaction mixture was cooled to RT, H_2O (200 mL) was added, and the aqueous solution was extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with H_2O (2 x 200 mL) and brine (100 ml), and dried over $MgSO_4$. After removal of the drying agent by filtration, the solvent was removed *in vacuo*. The resulting white solid was suspended in Et_2O (50 mL) and the pure product **289** (5.9 g, 65%) was isolated by suction filtration. The mother liquor was concentrated *in vacuo*, and the resulting white solid was recrystallised from Et_2O/Petrol. A further crop of pure **289** (2.27 g) was isolated thereafter. The combined overall yield of **289** = 8.17 g (88%). M.p. 130°C; $[\alpha]_D$ +34.1 ° (*c* 0.5, CH_2Cl_2); IR (KBr) 3423 (s), 2106 (s), 1736 (s), 1514 (s), 1458 (m), 1404 (m), 1374 (m), 1350 (m), 1315 (m), 1267 (s), 1221 (s), 1129 (s), 1091 (s), 1063 (s), 1048 (s), 1024 (s), 988 (s), 956 (s), 933 (m), 894 (m), 825 (m), 763 (m), 700 (m); ^{1}H-NMR (500 MHz, $CDCl_3$, 298 K) δ 7.43-7.38 (m, 2 H, arom.), 7.37-7.30 (m, 3 H, arom.), 5.64 (d, *J*= 9.0 Hz, 1 H, -NHCO$_2$Me), 5.61 (s, 1 H, Ph-CH-), 4.66 (s, 1 H, H1), 4.41 (m, 1 H, H3), 4.27 (dd, *J* = 10.1, 4.5 Hz, 1 H, H6), 3.98 (dd, *J* = 9.8, 4.0 Hz, 1 H, H4), 3.92 (m, 1 H, H5), 3.88 (s, 1 H, H2), 3.81 (dd, *J* = 10.2, 10.0 Hz, 1 H, H6), 3.67 (s, 3 H, -CO$_2$CH$_3$), 3.42 (s, 3 H, -OCH$_3$); ^{13}C-NMR (125 MHz, $CDCl_3$, 298 K) δ 156.6 (C=O), 137.0 (arom.), 128.9 (arom.), 128.2 (arom.), 126.0- (arom.), 101.6 (Ph-CH-), 99.2 (C1), 74.0 (C4), 68.9 (C6), 61.2 (C2), 59.2 (C5), 55.7 (-OCH$_3$), 52.3 (-CO$_2$CH$_3$), 49.3 (C3). HRMS Calcd for $C_{16}H_{21}N_4O_6$ $(M+H)^+$: *m/z* 365.14610. Found: *m/z* 365.14552. Anal. for $C_{16}H_{20}N_4O_6$. Calcd. C: 52.74; H: 5.53; N: 15.38. Found. C: 52.90; H: 5.25; N: 15.10.

Methyl 2-azido-2,3-dideoxy-3-methoxycarbonylamino-α-D-altropyranoside (287)



To a solution of the benzylidene acetal **289** (640 mg, 1.76 mmol) in anhydrous methanol (20 mL) was added acetyl chloride (380 µL, 5.27 mmol) dropwise. After the end of the addition, the mixture was stirred at room temperature for 30 minutes. The reaction was quenched with sat. aq. $NaHCO_3$ (5 mL), and the solution was extracted with AcOEt (3 x 20 mL). The combined organic layer was washed with brine (10 mL) and dried ($MgSO_4$). After concentration under vacuum, the residue was purified by SiO_2 flash chromatography (AcOEt/Petrol 85:15) to give diol **287** (457 mg, 94%) as a colourless oil which solidifies upon standing. $[\alpha]_D$ +26.0 ° (*c* 0.5, CH_3Cl_3); IR (neat) 3419 (br s), 2112 (s), 1636 (m), 1448 (w), 1320 (m), 1253 (m), 1142 (m), 1110 (m), 1079 (m), 1052 (m), 981 (w), 954 (w), 893 (w), 860 (m), 758 (m), 701 (w) ; ^{1}H-NMR (400 MHz, $CDCl_3$, 298 K) δ 5.93 (d, *J* = 8.2 Hz, 1 H, NH), 4.67 (s, 1 H, H1), 4.25 (t, *J* = 4.0 Hz, 1 H, H3), 4.02 (dd, *J* = 13.9, 4.2 Hz, 1 H, H4), 3.88 (dd, *J* = 11.9, 3.7 Hz, 1 H, H6), 3.83 (dd, *J* = 11.9, 4.7 Hz, 1 H, H6), 3.73 (m, 1 H, H2), 3.71 (s, 3 H, -OMe), 3.69 (m, 1 H, H5), 3.44 (s, 3 H, -OMe), 2.63 (br s, 2 H, -OH); ^{13}C-NMR (125 MHz, $CDCl_3$, 298 K) δ 158.1 (C=O), 98.4 (C1), 68.7 (C=O), 64.5 (C4), 62.5 (C6), 60.7 (C2), 55.6 (-OMe), 52.7 (-OMe), 51.6 (C3). HRMS Calcd for $C_9H_{17}N_4O_6$ $(M+H)^+$: *m/z* 277.11480 Found: *m/z* 277.11491.

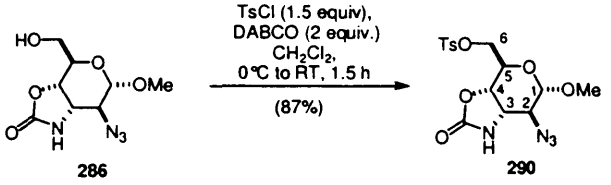
Oxazolidinone 286



To a solution of diol **287** (207 mg, 0.499 mmol) in freshly distilled THF (10 mL) under N_2 was added sodium hydride (60% in mineral oil, 100 mg, 2.50 mmol) in one portion. After 30 minutes stirring at room temperature, water (5 mL) was added to quench the reaction. The mixture was extracted with AcOEt (3 x 10 mL). The combined organic layer was washed with brine (2 mL) and dried ($MgSO_4$). After concentration under vacuum, the residue was purified by SiO_2 flash chromatography (AcOEt/Petrol 8:2 to 10:0) to give oxazolidinone **286** (192 mg, 100%) as a colourless oil. $[\alpha]_D$ +42.4 ° (*c* 0.21, CH_3Cl_3); IR (neat) 3420 (r s), 2118 (s), 1752 (s), 1637 (w), 1399 (w), 1336 (m), 1101 (m), 1048 (s), 987 (w), 956 (w), 760 (m); ^{1}H-NMR (400

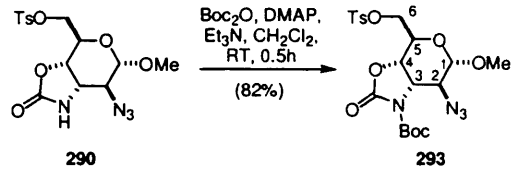
MHz, DMSO-d_6, 298 K) δ 8.42 (s, 1 H, -NH-), 4.99 (br s, 1 H, -OH), 4.55 (d, *J* = 6.9 Hz, 1 H, H1), 4.52 (t, *J* = 9.0 Hz, 1 H, H4), 3.89 (dd, *J* = 10.1, 7.0 Hz, 1 H, H2), 3.81 (ddd, *J* = 8.3, 5.5, 2.2 Hz, 1 H, H5), 3.61 (dd, J = 9.5, 9.4 Hz, 1 H, H3), 3.56 (m, 1 H, H6), 3.46 (m, 1 H, H6); ^{13}C-NMR (125 MHz, DMSO-d_6, 298 K) δ 158.6 (C=O), 101.5 (C1), 72.2 (C4), 70.3 (C3), 64.4 (C5), 62.6 (C6), 56.2 (-OMe), 52.6 (C2); HRMS Calcd for $C_8H_{13}N_4O_5$ $(M+H)^+$: *m/z* 245.08859. Found: *m/z* 245.08826.

Azido-oxazolidinone 290



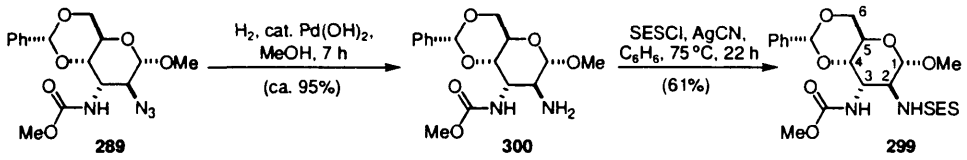
To a solution of alcohol **286** (1.97 g, 8.06 mmol) and DABCO (1.81 g, 16.1 mmol) in CH_2Cl_2 (80 mL) at 0°C was added *p*-toluenesulfonyl chloride (2.31 g, 12.1mmol) in several portions over 30 minutes under stirring. After the addition was complete, the cold bath was removed and the stirring was continued for 2 hours. Water (20 mL) was then added. The layers were separated, and the aqueous layer was further extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layer was washed with sat. aq. NH_4Cl (40 mL), brine (20 mL), and dried ($MgSO_4$). After concentration *in vacuo*, the residue was purified by SiO_2 flash chromatography (AcOEt/Petrol 6:4) to afford the title compound (2.78 g, 87%) as a white solid. M.p. 94°C; $[\alpha]_D$ +50.8 ° (*c* 1, CH_3Cl_3); IR (neat) 3351 (br m), 3020 w), 2938 (m), 2841 (w), 2118 (s), 1767 (s), 1597 (m), 1495 (w), 1449 (w), 1364 (s), 1312 (w), 1288 (w), 1258 (w), 1229 (m), 1176 (s), 1144 (m), 1096 (m), 1052 (s), 991 (s), 913 (m), 876 (w), 818 (m), 760 (s), 668 (m), 588 (w), 555 (s), 517 (w);^{1}H-NMR (500 MHz, $CDCl_3$, 298 K) δ 7.81 (d, *J* = 8.3 Hz, 2 H, arom.), 7.37 (d, *J* = 8.1 Hz, 2 H, arom.), 6.12 (s, 1 H, -NH-), 4.62-4.57 (m, 2 H, H1 + H4), 4.25 (dd, *J* = 11.1, 2.5 Hz, 1 H, H6), 4.17 (dd, *J* = 11.1, 5.4 Hz, 1 H, H6), 4.07-4.04 (m, 1 H, H5), 3.60-3.58 (m, 2 H, H2 + H3), 3.44 (s, 3 H, -OMe), 2.46 (s, 3 H, Tos.); ^{13}C-NMR (125 MHz, $CDCl_3$, 298 K) δ 157.7 (C=O), 145.3 (arom.), 132.3 (arom.), 130.0 (arom.), 128.0 (arom.), 100.7 (C1), 71.6 (C4), 68.3 (C6), 67.5 (C5), 63.8 (C3), 55.7 (-OMe), 52.0 (C2), 21.6 (Tos.); HRMS Calcd for $C_{15}H_{19}N_4O_7S$ $(M+H)^+$: *m/z* 399.09744. Found: *m/z* 399.09768.

N-Boc oxazolidinone 293



To a solution of azide **290** (2.50 g, 6.27 mmol), triethylamine (4.4 mL, 31.4 mmol), and DMAP (77.0 mg, 0.627 mol) in CH_2Cl_2 (100 mL) was added di-*tert*-butyl dicarbonate (2.05 g, 9.41 mmol) in one portion. After 30 minutes stirring at room temperature, water (30 mL) was added. The layers were separated, and the aqeuous layer was further extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layer were washed with sat. aq. NH_4Cl (30 mL), brine (20 mL), and dried ($MgSO_4$). After concentration *in vacuo*, the residue was purified by SiO_2 flash chromatography (AcOEt/Petrol 3:7) to afford the title compound (2.57 g, 82%) as a white solid. M.p. 137°C; $[\alpha]_D$ +88.6 ° (*c* 1, CH_3Cl_3); IR (KBr) 2994 (s), 2940 (s), 2847 (w), 2265 (m), 2119 (s), 1846 (s), 1712 (s), 1597 (s), 1473 (w), 1456 (s), 1332 (s), 1306 (s), 1257 (s), 1195 (s), 1116 (s), 1060 (s), 999 (s), 956 (s), 914 (s), 894 (m), 859 (m), 828 (s), 788 (s), 766 (s), 742 (s), 665 (s), 636 (w), 597 (m), 552 (s); ^{1}H-NMR (500 MHz, $CDCl_3$, 298 K) δ 7.77 (d, *J* = 8.3 Hz, 2 H, arom.), 7.34 (d, *J* = 8.0 Hz, 2 H, arom.), 4.60 (d, *J* = 5.0 Hz, 1 H, H1), 4.51 (dd, *J* = 8.2, 8.2 Hz, 1 H, H4), 4.27 (dd, *J* = 8.0, 8.0 Hz, 1 H, H3), 4.22 (dd, *J* = 11.1, 3.0 Hz, 1 H, H6), 4.15 (dd, *J* = 11.1, 5.1 Hz, 1 H, H6), 3.99 (m, 1 H, H5), 3.76 (dd, *J* = 8.1, 5.0 Hz, 1 H, H2), 3.37 (s, 3 H, -OMe), 2.44 (s, 3 H, Tos), 1.53 (s, 9 H, Boc); ^{13}C-NMR (125 MHz, $CDCl_3$, 298 K) δ 150.8 (C=O), 148.8 (C=O), 145.4 (arom.), 132.4 (arom.), 130.0 (arom.), 128.0 (arom.), 100.0 (C1), 85.1 (Boc), 68.6 (C4), 68.0 (C6), 67.0 (C5), 60.5 (C2), 55.9 (-OMe), 54.5 (C3), 27.8 (Boc), 21.7 (Tos.); HRMS Calcd for $C_{20}H_{27}N_4O_9S$ $(M)^+$: *m/z* 499.14986. Found: *m/z* 499.15022.

Methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-methoxycarbonylamino-2-trimethylsilyl-ethylsulfonamido-α-D-altropyranoside (299)

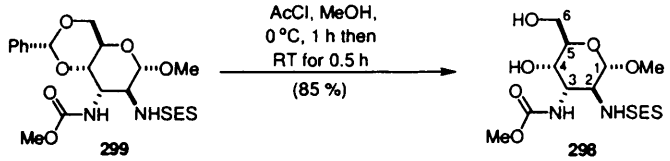


A suspension of 20% $Pd(OH)_2$ on C (Aldrich, wet type) (2.7 g, 2.6 mmol) and azide **289** (9.4 g, 26 mmol) were suspended in MeOH (280 mL) and the reaction vessel was sequentially evacuated and purged with H_2 gas five times before being allowed to stir vigorously under a

hydrogen atmosphere (1 atm) at room temperature for 3 h. The suspension was then filtered through a pad of Celite® and the solvent concentrated *in vacuo*. The resulting oil **300** (8.3 g) was sufficiently pure for use in the next step and was not purified any further.

To a mixture of amine **300** (10.4 g, 30.7 mmol) and AgCN (6.2 g, 46.1 mmol) in freshly distilled C_6H_6 was added SESCl (9.3 g, 46.1 mmol) in one portion. The reaction mixture was heated at 75 °C for 22 h and then cooled to room temperature before being filtered through Celite®. The filtrate was concentrated *in vacuo* and the crude residue purified by SiO_2 flash chromatography with 3:1 Petrol:EtOAc as eluent. Compound **299** (9.4 g, 61%) was obtained as a pale yellow oil. $[\alpha]_D$ +18.2 ° (*c* 0.5, CH_2Cl_2); IR (Neat) 3427 (w), 3267 (br w), 3016 (w), 2954 (m), 1721 (s), 1517 (s), 1455 (m), 1413 (w), 1376 (w), 1354 (w), 1324 (s), 1252 (s), 1147 (s), 1108 (s), 1070 (m), 1045 (s), 963 (w), 921 (m), 890 (m), 860 (s), 841 (s), 757 (s), 700 (m), 664 (w), 541 (w), 510 (w); ^{1}H-NMR (400 MHz, toluene-d_8, 363.8 K) δ 7.41-7.38 (m, 2 H, arom.), 7.09-6.97 (m, 3 H, arom.), 5.38 (s, 1 H, Ph-C<u>H</u>-), 5.34 (br d, *J* = 8.6 Hz, 1 H, -N<u>H</u>CO_2Me), 4.76 (d, *J* = 9.4 Hz, 1 H, -N<u>H</u>Ses), 4.62 (s, 1 H, H1), 4.30 (m, 1 H, H3), 4.00 (dd, *J* = 10.2, 5.0 Hz, 1 H, H6); 3.90 (d, *J* = 8.4, 1.3 Hz, 1 H, H2), 3.72 (ddd, *J* = 10.0, 9.9, 5.0, 4.9 Hz, 1 H, H5), 3.58 (dd, *J* = 10.0, 4.7 Hz, 1 H, H4), 3.52 (dd, *J* = 10.1, 10.1 Hz, 1H, H6), 3.33 (s, 3 H, -CO_2C<u>H</u>$_3$), 2.99 (dd, *J* = 9.2, 8.3 Hz, 2 H, Ses), 2.92 (s, 3 H, -OC<u>H</u>$_3$), 1.06 (m, 2 H, Ses), -0.10 (s, 9 H, -TMS); ^{13}C-NMR partial spectrum(125 MHz, toluene-d_8, 298 K) δ 156.9 (C=O), 138.1 (arom.), 126.7 (arom.), 102.4 (C1), 102.1 (Ph-<u>C</u>H-), 74.1 (C4), 69.2 (C6), 59.2 (C5), 55.3 (C3), 55.2 (-O<u>C</u>H$_3$), 51.8 (-CO_2<u>C</u>H$_3$), 51.7 (C2), 50.2 (Ses), 11.0 (Ses), -2.1 (-TMS). HRMS Calcd for $C_{21}H_{34}N_2O_8SSiNa$ $(M+Na)^+$: *m/z* 525.17027. Found: *m/z* 525.16969.

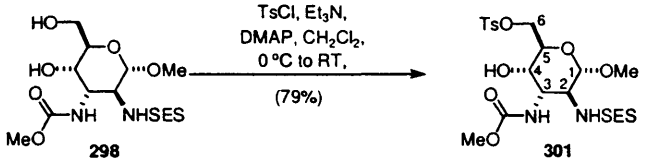
Methyl 2,3-dideoxy-3-methoxycarbonylamino-2-trimethylsilylethylsulfonamido-α-D-altropyranoside (298)



To a stirred solution of the protected diamino-sugar **299** (29.2 g, 58.1 mmol) in dry MeOH (290 mL) at 0 °C was added AcCl (12.4 mL, 174 mmol) dropwise over 40 min. The reactants were stirred at 0 °C for 1 h, and then allowed to warm to RT for 0.5 h. Solid $NaHCO_3$ was added until pH7 was attained, and the solvents removed *in vacuo*. The residue was taken up in EtOAc (300 mL), and the solution washed with H_2O (200 mL). The aqueous layer was extracted further with EtOAc (3 x 100 mL). The combined organic layers were washed successively with brine (200 mL), and dried over $MgSO_4$. After filtration and concentration *in vacuo*, the residue was purified by SiO_2 flash chromatography initially with 2:3 EtOAc/Petrol to

remove faster moving by-products, and then with EtOAc to elute the product **298** (20.4g, 85%) as an oil. $[\alpha]_D$ +35.6 ° (*c* 0.5, CH_2Cl_2); IR (Neat) 3410 (very br, s), 2954 (s), 1711 (s), 1525 (s), 1321 (s), 1252 (s), 1137 (s), 1108 (s), 1053 (s), 862 (m), 841 (m), 757 (w); ^{1}H-NMR (500 MHz, $CDCl_3$, 298 K) δ 5.97 (d, *J* = 8.0 Hz, 1 H, -NHSes), 5.75 (br s, 1 H, -NHCO$_2$Me), 4.67 (s, 1H, H1), 4.18 (m, 1 H, H3), 4.04 (dd, *J* = 9.7, 4.2 Hz, 1 H, H4), 3.89 (dd, *J* = 12.0, 3.3 Hz, 1 H, H6), 3.83 (dd, *J* = 12.0, 3.0 Hz, 1 H, H6), 3.68 (s, 3 H, -CO$_2$CH$_3$), 3.64 (m, 2 H, H2 + H5), 3.40 (s, 3 H, -OCH$_3$), 2.96 (m, 2 H, Ses), 2.48 (br s, 2 H, -OH), 0.99 (m, 2 H, Ses), 0.05 (s, 9 H, -TMS); ^{13}C-NMR (125 MHz, $CDCl_3$, 298 K) δ 158.1 (C=O), 101.1 (C1), 69.0 (C5), 63.4 (C4), 61.7 (C6), 55.6 (-OCH$_3$), 54.4 (C2), 53.1 (C3), 52.7 (-CO$_2$CH$_3$), 50.1 (Ses), 10.4 (Ses), -2.0 (-TMS). HRMS Calcd for $C_{14}H_{30}N_2O_8SSiNa$ $(M+Na)^+$: *m/z* 437.13898. Found: *m/z* 437.13846.

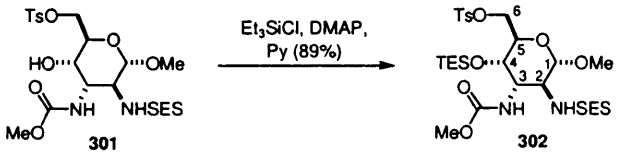
Methyl 2,3-dideoxy-3-methoxycarbonylamino-6-*O*-toluenesulphonyl-2-trimethylsilylethylsulfonamido-α-D-altropyranoside (301)



To a mixture of the diol **298** (15.5 g 37.4 mmol) and 4-dimethylaminopyridine (457 mg, 3.74 mol) in dry CH_2Cl_2 (190 mL) was added Et_3N (53 mL, 374 mmol). The reactants were cooled to 0 °C whereafter TsCl (7.46 g, 39.3 mmol) (freshly recrystallised from C_6H_6) was added portionwise over 1 h. Stirring was continued at 0 °C for a further 3 h, before the cooling-bath was removed, and the reaction mixture was allowed to warm to RT, where it was maintained for a further 13 h. Saturated aq. NH_4Cl (200 mL) was then added, and the biphasic mixture separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL), and the combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and filtered. The solvent was then removed *in vacuo* and the crude residue purified by SiO_2 flash chromatography (gradient elution 3:2 Petrol:EtOAc to EtOAc) to give **301** (16.9 g, 79%) as a white foam. $[\alpha]_D$ +22.2 ° (*c* 0.5, CH_2Cl_2); IR (Neat) 3412 (br m), 2955 (m), 1708 (s), 1598 (w), 1522 (s), 1452 (w), 1362 (s), 1324 (s), 1288 (w), 1253 (s), 1175 (s), 1140 (s), 1099 (s), 1055 (s), 981 (m), 839 (s), 758 (s); ^{1}H-NMR (400 MHz, $CDCl_3$, 328 K) δ 7.79 (d, *J* = 8.4 Hz, 2 H, Ts), 7.32 (d, *J* = 8.0 Hz, 2 H, Ts), 5.85 (d, *J* = 8.7 Hz, 1 H, -NHCO$_2$Me), 4.85 (d, *J* = 9.5 Hz, 1 H, -NHSes), 4.60 (s, 1 H, H1), 4.36 (dd, *J* = 11.2, 2.1 Hz, 1H), 4.25 (dd, *J* = 11.2, 5.3 Hz, 1 H, H6), 4.16 (m, 1 H,), 3.86-3.74 (m, 3 H,), 3.67 (s, 3 H, -CO$_2$CH$_3$), 3.37 (s, 3 H, -OCH$_3$), 2.96 (m, 2 H, Ses), 2.86 (br s, 1H), 2.42 (s, 3 H, Ts), 1.01 (m, 2 H, Ses), 0.06 (s, 9H); ^{13}C-NMR (125 MHz, $CDCl_3$, 298 K) δ 158.2 (C=O), 145.0 (arom.), 132.7 (arom.), 129.9 (arom.), 128.0 (arom.), 100.8 (C1), 69.2 (C6), 67.1 (C5), 63.9 (C4), 55.7 (-OCH$_3$), 54.0 (C2), 52.9 (C3), 52.8 (-CO$_2$CH$_3$), 50.4 (Ses), 21.6 (Ts), 10.5

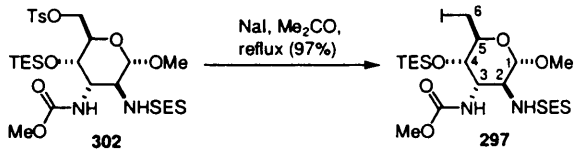
(Ses), -2.0 (-TMS). HRMS Calcd for $C_{21}H_{36}N_2O_{10}S_2SiNa$ $(M+Na)^+$: *m/z* 591.14783. Found: *m/z* 591.14793.

Methyl 2,3-dideoxy-3-methoxycarbonylamino-6-*O*-toluenesulphonyl-4-*O*-triethyl-silyl-2-trimethylsilylethyl-sulfonamido-α-D-altropyranoside (302)



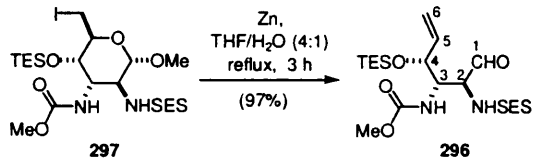
To a stirred solution of **301** (22.5 g, 39.6 mmol) and 4-dimethylaminopyridine (484 mg, 3.96 mmol) in dry pyridine (200 mL) was added chlorotriethylsilane (9.96 mL, 59.3 mmol) dropwise over 5 min. The reactants were stirred at RT for 19 h, whereafter the solvent was *removed in vacuo*. The residue was taken up in EtOAc (200 mL) and sat. aq. NH_4Cl (200 mL) was added. The organic layer was separated. The aqueous layer was extracted with EtOAc (3 x 200 mL), and the combined organic layers were washed with brine (50 mL) before being dried ($MgSO_4$) and filtered. The solvent was removed *in vacuo* and the crude residue purified by SiO_2 flash chromatography (gradient elution 4:1 Petrol:EtOAc to EtOAc) to give **302** (24.1 g, 89%) as an oil. $[\alpha]_D$ +42.6 ° (*c* 0.31, CH_2Cl_2); IR (Neat) 3434 (br m), 2955 (s), 1726 (s), 1597 (w), 1517 (s), 1455 (w), 1366 (s), 1324 (s), 1251 (s), 1176 (s), 1138 (s), 1110 (s), 1059 (s), 1018 (m), 929 (m), 862 (s), 837 (s), 742 (m), 665 (w); ^{1}H-NMR (500 MHz, $CDCl_3$, 298 K) δ 7.78 (d, *J* = 8.3 Hz, 2 H, Ts), 7.34 (d, *J* = 8.6 Hz, 2 H, Ts), 5.44 (d, *J* = 9.6 Hz, 1 H, -NHCO$_2$Me), 4.67 (d, *J* = 9.7 Hz, 1 H, -NHSes), 4.52 (d, *J* = 2.4 Hz, 1 H, H1), 4.25 (dd, *J* = 10.9, 1.8 Hz, 1 H, H6), 4.14 (dd, *J* = 10.8, 5.6 Hz, 1 H, H6), 3.98 (m, 1 H, H3), 3.82 (m, 1 H, H4), 3.74 (m, 1H, H5), 3.64 (s, 3 H, -CO$_2$CH$_3$) superimposed upon 3.62 (m, 1 H, H2), 3.31 (s, 3 H, -OCH$_3$), 2.97 (m, 2 H, Ses), 2.43 (s, 3 H, Ts), 1.01 (m, 2 H, Ses), 0.88 (t, *J* = 8.0 Hz, 9 H, Tes), 0.56 (m, 6 H, Tes), 0.05 (s, 9H, -TMS); ^{13}C-NMR (125 MHz, $CDCl_3$, 298 K) δ 156.9 (C=O), 145.0 (arom.), 133.0 (arom.), 129.9 (arom.), 128.0 (arom.), 101.4 (C1), 69.0 (C6), 68.3 (C5), 64.4 (C4), 55.7 (-OCH$_3$), 54.3 (C2), 52.8 (C3), 52.3 (-CO$_2$CH$_3$), 50.2 (Ses), 21.6 (Ts), 10.6 (Ses), 6.7 (Tes), 4.6 (TES), -2.0 (-TMS). HRMS Calcd for $C_{27}H_{50}N_2O_{10}S_2Si_2Na$ $(M+Na)^+$: *m/z* 705.23429. Found: *m/z* 705.23488.

Methyl 6-iodo-3-methoxycarbonylamino-2,3,6-trideoxy-4-*O*-triethylsilyl-2-trimethylsilylethylsulfonamido-α-D-altropyranoside (297)



To a stirred solution of **302** (13 g, 19 mmol) in acetone (380 mL) was added NaI (28.5 g, 190 mmol). The reaction mixture was heated at reflux for 24 h, the solvent removed *in vacuo*, and the residue suspended in EtOAc (400 ml), washed with H_2O (200 mL), brine (50 mL) and then dried over $MgSO_4$. Filtration, and concentration of the filtate *in vacuo*, gave a residue that was purified by SiO_2 flash chromatography (gradient elution 85:15 to 7:3 Petrol:EtOAc). The title compound **297** (11.8 g, 98%) was obtained as a colourless oil. $[\alpha]_D$ +40.3 ° (*c* 0.27, CH_2Cl_2); IR (Neat) 3434 (m), 3267 (m), 2956 (s), 2913 (s), 2879 (s), 2840 (w), 1729 (s), 1517 (s), 1451 (m), 1324 (s),1251 (s), 1136 (s), 1026 (s), 851 (s), 800 (m), 742 (s), 699 (w); ^{1}H-NMR (500 MHz, $CDCl_3$, 298 K) δ 5.52 (d, *J* = 9.6 Hz, 1 H, -NHCO$_2$Me), 4.82 (d, *J* = 10.1 Hz, 1 H, -NHSes), 4.67 (d, *J* = 2.0 Hz, 1 H, H1), 4.01 (m, 1 H, H3), 3.75 (m, 1 H, H4), 3.67 (m, 1 H, H2) superimposed upon 3.65 (s, 3 H, -CO$_2$CH$_3$), 3.48 (m, 2 H, H5 + H6) superimposed upon 3.45 (s, 3 H, -OCH$_3$), 3.27 (dd, *J* = 11.1, 8.0 Hz, 1 H, H6), 2.99 (m, 2 H, Ses), 1.03 (m, 2 H, Ses), 0.94 (t, *J* = 8.0 Hz, 9 H, Tes), 0.65 (m, 6 H, Tes), 0.04 (s, 9 H, Ses); ^{13}C-NMR (125 MHz, $CDCl_3$, 298 K) δ 156.9 (C=O), 101.5 (C1), 69.3 (C5), 68.5 (C4), 56.0 (-OCH$_3$), 54.6 (C2), 53.0 (C3), 52.3 (-CO$_2$CH$_3$), 50.3 (Ses), 10.6 (Ses), 7.1 (C6), 6.8 (Tes), 4.7 (Tes), -2.0 (-TMS). HRMS Calcd for $C_{20}H_{43}IN_2O_7SSi_2Na$ $(M+Na)^+$: *m/z* 661.12718. Found: *m/z* 661.12809.

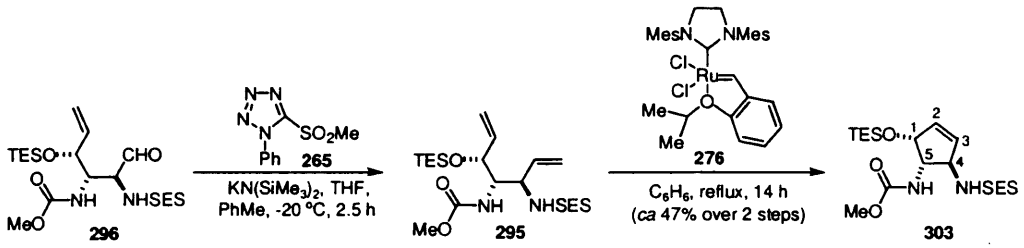
Aldehyde 296



To a stirred solution of iodide **297** (12.1g, 19 mmol) in THF:$H_2$0 (4:1, 380 mL) was added Zn dust (24.9 g, 0.380 mol) (Aldrich 20,998-8) and the mixture heated at reflux for 3 h. The suspension was then cooled, diluted with EtOAc (400 mL) and filtered through Celite®, and the filtrate thereafter washed with brine (2 x 100 mL), before being dried over $MgSO_4$. After filtration, the solvent was removed *in vacuo* and the residue purified by SiO_2 flash

chromatography with 7:3 Petrol:EtOAc to give **296** as a colourless oil (8.43g, 92%). $[\alpha]_D$ +10.6 ° (*c* 0.4, CH_2Cl_2); IR (Neat) 3334 (br m), 2956 (s), 2913 (s), 2878 (s), 1728 (s), 1644 (w), 1535 (s), 1458 (s), 1419 (s), 1329 (s), 1250 (s), 1171 (m), 1145 (s), 1101 (s), 1062 (s) 1010 (m), 861 (s), 840 (s), 744 (s); Mixture of 2 rotamers: α and β (3/1) ^{1}H-NMR (500 MHz, toluene-d_8, 363 K) δ 9.32 (s, 1 H, H1 α), 9.23 (s, 1 H, H1 β), 5.65 (ddd, *J* = 17.3, 10.4, 7.0 Hz, 1 H, H5 α), 5.60 (m, 1 H, H5 β), 5.17 (br d, *J* = 6.9 Hz, 1 H, -NHSes), 5.05 (ddd, *J* = 17.2, 1.3 Hz, 1 H, H6 α), 4.99 (ddd, *J* = 17.2, 1.3 Hz, H6 β), 4.94 (ddd, *J* = 10.4, 1.3 Hz, H6 α), 4.90 (m, 1H, H6 β), 4.71 (d, *J* = 8.0 Hz, 1 H, -NHCO$_2$Me), 4.30 (dd, *J* = 7.2, 3.5 Hz, 1 H, H2 α), 4.25 (m, 1 H, H4 α), 4.15 and 4.10 (m, 2 H, H2 β + H4 β), 3.99 (m, 1 H, H3 α), 3.44 (s, 3 H, -CO$_2$CH$_3$ β), 3.40 (s, 3 H, -CO$_2$CH$_3$ α), 2.83 (m, 2 H, Ses α), 2.80 (m, 2 H, Ses β), 1.02 (m, 4 H, Ses α,β), 0.89 (t, *J* = 8.1 Hz, 9 H, Tes α), 0.83 (t, *J* = 7.9 Hz, 9 H, Tes β), 0.55 (q, *J* = 8.0 Hz, 6 H, Tes α), 0.46 (q, *J* = 8.0 Hz, 6 H, Tes β), -0.15 (s, 9 H, -TMS α), -0.16 (s, 9 H, -TMS β); ^{13}C-NMR (125 MHz, toluene-d_8, 363 K) δ 196.9 (C1 α), 195.2 (C1 β), 137.7 (C5), 117.7 (C6), 74.7 (C4), 63.5 (C2 β), 62.8 (C2 α), 55.7 (C3), 51.5 (-CO$_2$CH$_3$), 50.0 (Ses α), 49.4 (Ses β), 10.5 (Ses), 6.2 (Tes α), 6.1 (Tes β), 5.0 (Tes α), 4.9 (Tes β), -2.8 (-TMS). HRMS Calcd for $C_{19}H_{40}N_2O_6SSi_2Na$ $(M+Na)^+$: *m/z* 481.22237. Found: *m/z* 481.22286.

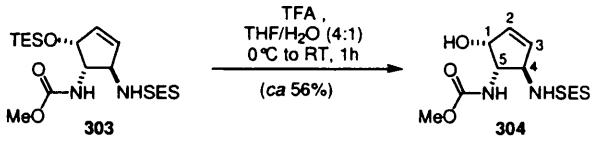
Cyclopentene-Oxazolidinone 151 and Cyclopentenol 304.



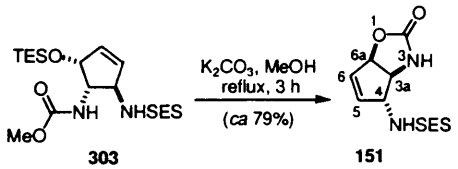
To a stirred solution of sulfone **263** (5.48 g, 24.5 mmol) and aldehyde **296** (8.4 g, 17.5 mmol) in freshly distilled THF (75 mL) at –20 °C was added potassium hexamethyldisilazide (0.5 M soln in PhMe, 126 mL, 63.0 mmol) dropwise over 30 min. The mixture was stirred at –20 °C for 2 h before H_2O (50 mL) was added, and the cooling bath removed. Most of the THF was removed by evaporation *in vacuo*, and the product extracted from the aqueous solution with EtOAc (400 mL). The combined organic layers were washed with H_2O (100 ml), 1M aq. HCl (2 x 50 mL), sat. aq. $NaHCO_3$ (50 mL), brine (100 mL) and dried over $MgSO_4$. Filtration, concentration *in vacuo*, and purification of the crude residue by SiO_2 flash chromatography with 85:15 Petrol:EtOAc provided **295** as a colourless oil (5.07 g) slightly contaminated by tetrazole by-product.

The slightly impure diene **295** and the Grubbs-Hoveyda catalyst **276** (130 mg, 0. 208 mmol) were dissolved in freshly distilled C_6H_6 (390 mL) and the reaction mixture heated at reflux for 14 h. The solvent was removed *in vacuo* and the crude residue partially purified by SiO_2

flash chromatography with 88:12 Petrol:EtOAc as eluent. Cyclopentene **303** (3.7 g) was obtained slightly contaminated with the aforementioned tetrazole derivative.



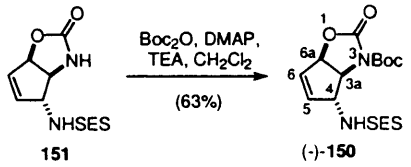
To a solution of **303** (960 mg, 2.13 mmol) in a mixture of THF (20 mL) and water (5 mL) at 0°C was added TFA (1.66 mL, 21.5 mmol) in a dropwise manner. The cold bath was then removed, and the mixture was stirred at room temperature. After 1 h, the mixture was cooled down to 0°C, and sat. aq. $NaHCO_3$ (70 mL) was carefully added to quench the reaction. The product of the reaction was extracted with AcOEt (3 x 20 mL). The combined organic layer was washed with brine and dried ($MgSO_4$). After concentration *in vacuo*, a white solid is obtained, which is washed with ether and dried under vaccum to afford **304** (399 mg, 20% over 3 steps from **296**) as a white solid. M.p. 179°C; $[\alpha]_D$ –150.3 ° (*c* 0.4, MeOH); IR (KBr) 3396 (s), 3243 (s), 3069 (m), 2955 (m), 1696 (s), 1558 (s), 1456 (s), 1414 (s), 1366 (w), 1326 (s), 1292 (s), 1250 (s), 1229 (m), 1184 (m), 1147 (s), 115 (s), 1090 (s), 1058 (m), 1003 (m), 933 (s), 896 (s), 840 (s), 784 (m), 740 (s), 655 (w), 536 (m) ; ^{1}H-NMR (500 MHz, DMSO-d_6, 298 K) δ 7.30 (d, *J* = 8.2 Hz, 1 H, -NHSes), 7.04 (d, *J* = 8.9 Hz, 1 H, -NHCO$_2$Me), 5.88 (br s, 1 H, H2), 5.76 (d, *J* = 5.3 Hz, 1 H, H1), 4.84 (d, *J* = 5.5 Hz, 1 H, -OH), 4.34 (br s, 1 H, H3), 4.26 (br s, 1 H, H5), 3.76 (ddd, *J* = 8.2, 6.7, 6.5 Hz, 1 H, H4), 3.53 (s, 3 H, -CO$_2$CH$_3$), 2.91 (m, 2 H, Ses), 0.86 (m, 2 H, Ses), 0.01 (s, 9 H, -TMS); ^{13}C-NMR (125 MHz, DMSO-d_6, 298 K) δ 156.7 (C=O), 136.2 (C1), 133.9 (C2), 70.9 (C3), 60.9 (C5), 59.39 (C4), 51.3 (-CO$_2$CH$_3$), 48.5 (Ses), 10.1 (Ses), -2.0 (-TMS); HRMS Calcd for $C_{12}H_{25}N_2O_5SSi$ $(M+H)^+$: *m/z* 337.12534. Found: *m/z* 337.12494.



To a solution of the slightly impure cyclopentene **303** (3.15 g) in MeOH (140 mL) was added K_2CO_3 (4.83 g, *ca.* 34.9 mmol) and the mixture heated at reflux for 2 h before being allowed to stand overnight for 11 h. The solvent was removed *in vacuo*, and the residue was taken up in EtOAc (150 mL) and H_2O (100 mL). The organic layers were separated and the aqueous fraction extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with H_2O (50 mL), brine (50 mL), and dried ($MgSO_4$). Filtration and concentration *in vacuo* gave a residue that was purified by SiO_2 flash chromatography with 3:2 EtOAc:Petrol to give pure **151** as a foam (1.9 g, 41% over 4 steps from **260**). $[\alpha]_D$ –65.7 ° (*c* 0.38, CH_2Cl_2); IR (Neat) 3350 (s),

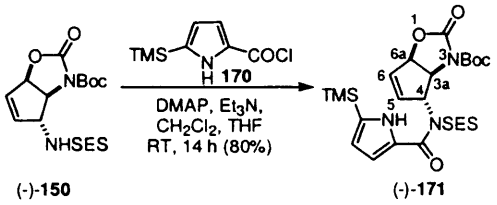
3286 (s), 2959 (m), 2897 (w), 1765 (s), 1716 (s), 1538 (w), 1454 (s), 1420 (s), 1321 (s), 1253 (s), 1212 (w), 1137 (s), 1043 (s), 947 (s), 836 (s), 775 (s); ^{1}H-NMR (500 MHz, DMSO-d_6, 298 K) δ 8.11 (s, 1 H, -NHCO-), 7.36 (s, 1 H, -NHSes), 6.02 (m, with appearance of a large s, 2 H, H5 + H6), 5.53 (m, 1 H, H6a), 4.17 (s, 1 H, H4), 4.01 (d, J = 7.1 Hz, 1 H, H3a), 2.96 (m, 2 H, Ses), 0.87 (m, 2 H, Ses), 0.04 (s, 9 H, -TMS); ^{13}C-NMR (125 MHz, DMSO-d_6, 298 K) δ 157.1 (C=O), 135.4 (alkene), 132.0 (alkene), 83.5 (C6a), 64.5 (C4), 60.6 (C3a), 48.2 (Ses), 10.0 (Ses), -1.9 (-TMS). HRMS Calcd for $C_{11}H_{21}N_2O_4SSiNa$ $(M+H)^+$: *m/z* 305.09912. Found: *m/z* 305.09997.

BOC-Cyclopentene oxazolidinone 150



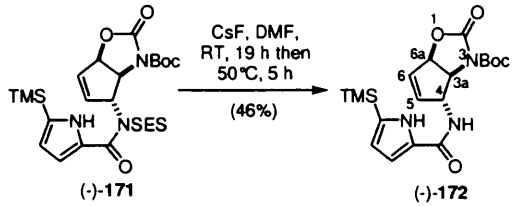
To a stirred solution of oxazolidinone **151** (1.22 g, 4.01 mmol), 4-dimethylaminopyridine (123 mg, 1 mmol), and Et_3N (0.62 ml, 4.4 mmol) in dry CH_2Cl_2 (80 mL) was added a solution of Boc_2O (963 mg, 4.41 mmol) in CH_2Cl_2 (1.1 mL) dropwise at RT over 10 min. The reactants were stirred at RT for 12 h, whereupon more Boc_2O (88 mg, 0.4 mmol) was added, and the stirring continued for a further 2 h. H_2O (40 mL) was added to the reaction mixture, and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL), and the combined organic layers washed with 1M aq. HCl (10 mL), sat. aq. $NaHCO_3$ (10 mL), dried ($MgSO_4$), and filtered. The solvent was removed *in vacuo* and the crude residue recrystallised from EtOAc/petrol to provide 17 (807 mg, 50%) as a white crystalline solid. The mother liquors were concentrated *in vacuo*, and the residue purified by SiO_2 flash chromatography with 3:2 Petrol:EtOAc to provide a further quantity of **150** (210 mg, 62% overall). M.p. 162°C; $[\alpha]_D$ –88.0 ° (*c* 0.22, CH_2Cl_2); IR (KBr) 3283 (s), 2979 (w), 1792 (s), 1724 (s), 1455 (m), 1366 (s), 1338 (s), 1251 (s), 1168 (s), 1138 (s), 1073 (s), 901 (m), 856 (s); ^{1}H-NMR (500 MHz, $CDCl_3$, 298 K) δ 6.14 (dd, J = 5.5, 2.1 Hz, 1 H, H5), 6.05 (ddd, J = 5.7, 1.7,1.5 Hz, 1 H, H6), 5.50 (br d, J = 7.4 Hz, 1 H, H6a), 4.60 (d, J = 7.9 Hz, 1 H, -NHSes), 4.53 (m, 2 H, H3 and H4), 3.10 (m, 2 H, Ses), 1.54 (s, 9H, Boc), 1.03 (m, 2 H, Ses), 0.05 (s, 9 H, TMS); ^{13}C-NMR (125 MHz, $CDCl_3$, 298 K) δ 150.4 (C=O), 150.2 (C=O), 136.5 (C5), 131.8 (C6), 85.0 (Boc), 80.1 (C6a), 65.1 (C3a), 63.6 (C4), 50.3 (Ses), 27.9 (Boc), 10.5 (Ses), -2.0 (TMS). HRMS Calcd for $C_{16}H_{28}N_2O_6SSiNa$ $(M+Na)^+$: *m/z* 427.13349. Found: *m/z* 427.13286.

5-TMS-Pyrrole-2-carboxamido-*N*-SES-Cyclopentene-Boc-Oxazolidinone 171



To a suspension of lithio 2-TMS-pyrrole-5-carboxylate (3.3 g, 20.2 mmol) in freshly distilled CH_2Cl_2 (30 mL) at 0 °C was added oxalyl chloride (1.8 mL, 20.4 mmol) followed by 4 drops of dry DMF. After 10 min, the ice-bath was removed, and the reactants were stirred at RT for 2 h. The resulting suspension of **170** and LiCl was taken up via a glass syringe (slightly greased) and added dropwise over 1.5 h via syringe pump (flow rate 20 mL/h) to a solution of the amide **150** (3.3 g, 8.16 mmol) and DMAP (100 mg, 0. 816 mmol) in dry THF (44 mL) and Et_3N (5.7 mL, 40.8 mol) at RT. After the addition was complete, TLC (7:3 petrol:EtOAc) analysis indicated that none of the starting amide **150** remained. Sat. aq. $NaHCO_3$ (23 mL) was added in one portion, and the mixture was partitioned between brine (75 mL) and CH_2Cl_2 (150 mL). The organic layer was separated, dried over $MgSO_4$, and filtered. The solvent was removed *in vacuo* and the residue was purified by SiO_2 flash chromatography with 4:1 petrol:EtOAc to give **171** (3.7 g, 80%) as a white foam. $[\alpha]_D$ -127 ° (*c* 0.5, CH_2Cl_2); IR (KBr) 3417 (m), 2959 (m), 2902 (w), 1817 (s), 1723 (s), 1629 (s), 1528 (w), 1440 (s), 1350 (s), 1277 (s), 1253 (s), 1188 (s), 1140 (s), 1054 (s), 843 (s), 751 (s), 699 (m); ^{1}H-NMR (500 MHz, $CDCl_3$, 298 K) δ 9.36 (br s, 1 H, NH), 6.81 (dd, *J* = 3.8, 2.3 Hz, 1 H, arom), 6.42 (dd, *J* = 3.8, 2.7 Hz, 1 H, arom.), 6.17 (dd, *J* = 5.9, 2.1 Hz, 1 H, H5), 6.13 (m, 1 H, H6), 5.62 (m, 2 H, H4 and H6a), 4.98 (dd, *J* = 7.4, 1.4 Hz, 1 H, H3a), 3.59 (ddd, *J* = 14.1, 13.8, 4.5 Hz, 1 H, Ses), 3.46 (ddd, *J* = 14.1, 13.8, 4.3 Hz, 1 H, Ses), 1.38 (s, 9 H, Boc), 1.08 (ddd, *J* = 13.7, 9.6 Hz, 1 H, Ses) superimposed upon 1.01 (ddd, *J* = 13.7 Hz, 4.7 Hz, 1 H, Ses), 0.26 (s, 9 H, TMS), 0.03 (s, 9 H, Ses); ^{13}C-NMR (125 MHz, $CDCl_3$, 298 K) δ 162.6 (C=O), 150.9 (C=O), 149.6 (C=O), 140.3 (arom.), 134.5 (alkene), 133.1 (alkene), 126.9 (arom.), 119.2 (arom.), 117.3 (arom.), 84.7 (Boc), 81.4 (C6a), 71.3 (C4), 61.5 (C3a), 52.9 (Ses), 27.7 (Boc), 9.9 (Ses), -1.4 (TMS), -2.0 (Ses). HRMS Calcd for $C_{24}H_{39}N_3O_7SSi_2$ $(M)^+$: *m/z* 569.20471. Found: *m/z* 569.20520.

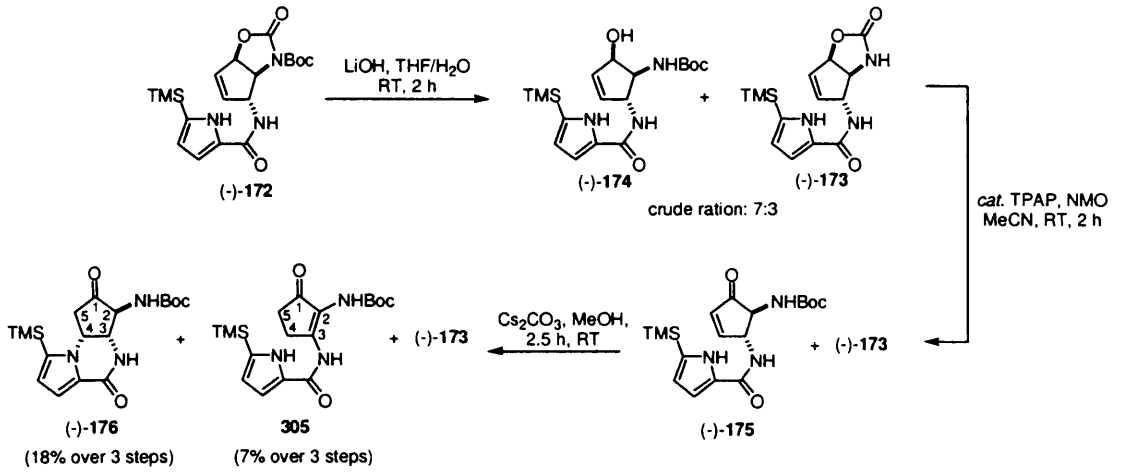
5-TMS-Pyrrole-2-carboxamido- Cyclopentene-Boc-Oxazolidinone 172



Protocol A. To a solution of the sulfonamide **171** (348 mg, 0.675 mmol) in dry DMF (3.5 mL) was added CsF (103 mg, 0.675 mmol) at RT and the mixture stirred at RT for 19 h before being heated at 50 °C for 1 h. After cooling to RT, H_2O (50 mL) was added and the aqueous solution was extracted with EtOAc (6 x 15 mL). The combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), and filtered. The solvent was then removed *in vacuo* and the residue was purified by SiO_2 flash chromatography with 3:2 Petrol/EtOAc to give **172** (169 mg, 68%) as a yellow oil; **171** (58 mg) was also recovered. Data for **172**: $[\alpha]_D$ -166 ° (*c* 0.274, CH_2Cl_2); IR (Neat) 3293 (w), 2957 (w), 1807 (s), 1725 (w), 1636 (m), 1550 (s), 1524 (m), 1365 (s), 1336 (s), 1252 (s), 1200 (s), 1155 (s), 1075 (s), 1041 (m), 842 (s), 756 (s) cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$, 298 K) δ 9.17 (br s, 1 H, NH), 6.57 (dd, *J* = 3.6, 2.3 Hz, 1 H, arom.), 6.35 (dd, *J* = 3.6, 2.7 Hz, 1 H, arom.), 6.31 (d, *J* = 7.9 Hz, 1 H, NH), 6.05 (s, 2 H, alkene), 5.61 (ddd, *J* = 7.7, 1.8, 1.0 Hz, 1 H, H6a), 4.92 (m, 1 H, H3a), 4.68 (dd, *J* = 7.6, 1.4 Hz, 1 H, H4), 1.50 (s, 9 H, Boc), 0.23 (s, 9 H, TMS); ^{13}C-NMR (125 MHz, $CDCl_3$, 298 K) δ 160.7 (C=O), 151.4 (C=O), 149.4 (C=O), 136.7 (alkene), 136.5 (arom), 130.8 (alkene), 128.5 (arom), 118.3 (arom.), 110.0 (arom.), 84.5 (Boc), 81.2 (C6a), 62.8 (C4), 62.7 (C3a), 27.9 (Boc), -1.2 (TMS). HRMS Calcd for $C_{19}H_{27}N_3O_5Si$ $(M+H)^+$: *m/z* 406.17981. Found: *m/z* 406.17997.

Larger Scale Protocol B. To a stirred solution of the sulfonamide (3.56 g, 6.25 mmol) in dry DMF (30 mL) was added CsF (950 mg, 6.25 mmol) at RT and the mixture stirred at RT for 17.5 h before being heated at 50 °C for 5 h. After cooling to RT, H_2O (500 mL) was added and the aqueous solution extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), and filtered. The solvent was then removed *in vacuo* and the residue was purified by SiO_2 flash chromatography with 3:2 Petrol/EtOAc to give **172** (1.17 g, 46%) as a yellow oil.

5-TMS-Pyrrole-2-carboxamido-Cyclopentene-Boc-Oxazolidinone 176



To a solution of the protected oxazolidinone **172** (1.12 g, 2.77 mmol) in THF/H_2O (9:1, 70 mL) was added LiOH.H_2O (0.93 g, 22.2 mmol) in one portion. The solution was vigorously stirred at RT for 2 h. Excess silica gel was added, and the solvents removed *in vacuo*. Application of the silicated sample to the top of a column containing SiO_2 followed by elution with EtOAc afforded **173** and **174** (1.06 g) as an essentially inseparable mixture. 500 MHz ^{1}H NMR analysis of the entire mixed sample of **173** and **174** indicated it was a 7:3 mixture enriched in **174**.

To a solution of the aforementioned mixture of **173** and **174** (*ca.* 2.64 mmol) in freshly distilled MeCN (53 mL) was added successively NMO (619 mg, 5.28 mmol), 4Å MS (*ca.* 4 g), and TPAP (93 mg, 0.264 mmol), and the solution vigorously stirred at RT for 2 h. The solvent was then removed *in vacuo*, the crude residue taken up in EtOAc (50 mL) and the solution filtered through a pad of Celite®, and the pad thoroughly washed with more EtOAc. The filtrate was concentrated *in vacuo*, and the residue partially purified by gradient elution SiO_2 flash chromatography (with 7:3 Petrol:EtOAc progressing to EtOAc) to give a mixture of **175** and **173** (530 mg, in *ca.* 3:1 ratio according to ^{1}H NMR analysis).

The aforementioned mixture of ketone **175** and oxazolidinone **173** (*ca.* 1.41 mmol) was dissolved in MeOH (140 mL) and Cs_2CO_3 (460 mg, 1.41 mmol) was added. The reactants were stirred vigorously at RT for 1 h whereafter a further quantity of Cs_2CO_3 (1.84 g, 4 equiv) was added. Stirring was continued for a further 1 h, whereupon TLC analysis indicated that two faster-moving products had formed and that the starting oxazolidinone **173** remained. The mixture was partitioned between EtOAc (560 mL) and brine (140 mL). The layers were separated and the organic layer dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by SiO_2 flash chromatography with 7:3 Petrol:EtOAc to give **305** (72 mg,

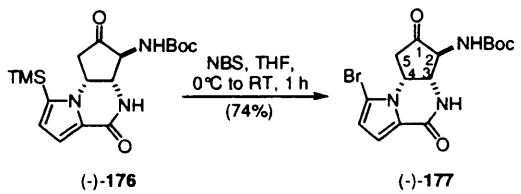
7% from **172**) initially as a white solid, followed by **176** (189 mg, 18% from **139**) as a colourless oil, and finally, recovered oxazolidinone **173** (130 mg) as a white solid.

The respective spectral data for **176** and **305** are presented below.

Enaminone/pyrrole **305**: IR (KBr) 3226 (s), 2957 (w), 1693 (s), 1662 (s), 1631 (s), 1545 (s), 1501 (s), 1426 (m), 1372 (s), 1308 (s), 1273 (s), 1248 (s), 1161 (s), 1057 (w), 964 (s), 843 (s), 736 (w); ^{1}H-NMR (500 MHz, $CDCl_3$, 298 K) δ 11.90 (s, 1 H, NH), 9.37 (s, 1 H, NH), 6.97 (dd, *J* = 4.5, 2.2 Hz, 1 H, arom.), 6.78 (br s, 1 H, NH), 6.45 (dd, *J* = 3.4, 2.8 Hz, 1 H, arom.), 3.33 (m, 2 H, $C\underline{H}_2$), 2.47 (m, 2 H, $C\underline{H}_2$), 1.50 (s, 9 H, Boc), 0.26 (s, 9 H, TMS); ^{13}C-NMR (125 MHz, $CDCl_3$, 298 K) δ 198.6 (C=O), 158.4 (C=O), 154.5 (C=O), 149.5 (alkene), 138.2 (alkene), 129.4 (arom.), 118.9 (arom.), 117.3 (arom.), 112.4 (arom.), 82.2 (Boc), 31.7 ($\underline{C}H_2$), 28.1 (Boc), 25.4 ($\underline{C}H_2$), -1.2 (TMS). HRMS Calcd for $C_{18}H_{27}N_3O_4Si$ $(M+H)^+$: *m/z* 378.18489. Found: *m/z* 378.18492.

Desired Tricycle **176**: $[\alpha]_D$ −134° (*c* 0.5 $CHCl_3$); IR (Neat) 3347 (br w), 2977 (w), 1765 (m), 1712 (m), 1665 (s), 1543 (m), 1366 (m), 1336 (m), 1251 (s), 1164 (s), 842 (s), 754 (s); ^{1}H-NMR (500 MHz, MeOD, 298 K) δ 6.92 (d, *J* = 3.8 Hz, 1 H, arom.), 6.43 (d, *J* = 3.8 Hz, 1 H, arom.), 5.13 (ddd, *J* = 9.0, 4.5 Hz, 1 H, H4), 4.79 (br d, *J* = 4.0 Hz, 1 H, H2), 4.59 (apparent t, *J* = 4.4 Hz, 1 H, H3), 2.96 (dd, *J* = 19.1, 10.2 Hz, 1 H, H5), 2.17 (dd, *J* = 19.1, 9.1 Hz, 1 H, H5), 1.48 (s, 9 H, Boc), 0.36 (s, 9 H, TMS); ^{13}C-NMR (125 MHz, MeOD, 298 K) δ 208.6 (C=O), 162.2 (C=O), 157.9 (C=O), 139.7 (arom.), 126.8 (arom.), 121.1 (arom.), 116.0 (arom.), 81.4 (Boc), 63.7 (C2), 56.2 (C3), 51.4 (C4), 41.6 (C5), 28.6 (Boc), -0.5 (TMS). HRMS Calcd for $C_{18}H_{27}N_3O_4Si$ $(M+H)^+$: *m/z* 378.18489. Found: *m/z* 387.18418.

Pyrrole Bromide 177

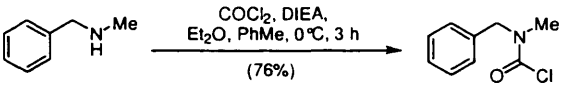


(-)-**176** (-)-**177**

To a stirred solution of the *N*-Boc-α-amino-ketone (-)-**176** (110 mg, 0.292 mmol) in freshly distilled THF (21 mL) at 0 °C was added *N*-bromosuccinimide (62 mg, 351 mmol) in one portion. The reactants were stirred at 0 °C for 1 h and then at RT for a further 5 h. Sat. aq. $NaHCO_3$ (20 mL) and sat. aq. $Na_2S_2O_3$ (5 ml) were added to the mixture, and the product **177**

extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), and filtered. The solvent was then removed *in vacuo*, and the crude residue purified by SiO_2 flash chromatography with 3:2 Petrol/EtOAc to give (-)-**177** (83 mg, 74%) as a colourless oil. $[\alpha]_D$ –112° in (*c* 0.66, MeOH); IR (Neat) 3334 (br w), 2979 (w), 1764 (s), 1711 (s), 1665 (s), 1554 (m), 1423 (s), 1378 (m), 1338 (s), 1251 (m), 1165 (s), 1062 (w), 751 (s); ^{1}H-NMR (500 MHz, MeOD, 298 K) δ 6.93 (d, *J* = 4.1 Hz, 1 H, arom.), 6.35 (d, *J* = 4.1 Hz, 1 H, arom.), 5.22 (ddd, *J* = 9.1, 4.8, 4.7 Hz, 1 H, H4), 4.74 (br d, 1 H, H2), 4.62 (apparent t, *J* = 4.6 Hz, 1 H, H3), 3.02 (dd, *J* = 19.1, 9.0 Hz, 1 H, H5), 2.13 (dd, *J* = 19.1, 9.2 Hz, 1 H, H5), 1.48 (s, 9 H, Boc); ^{13}C-NMR (125 MHz, MeOD, 298 K) δ 208.3 (C=O), 161.5 (C=O), 157.8 (C=O), 123.9 (arom.), 116.4 (arom.), 114.2 (arom.), 107.5 (arom.), 81.4 (Boc), 63.4 (C2), 55.5 (C3), 49.8 (C4), 39.8 (C5), 28.6 (Boc). HRMS Calcd for $C_{15}H_{18}N_3O_4{}^{79}Br$ $(M+H)^+$: *m/z* 384.05588. Found: *m/z* 384.05552.

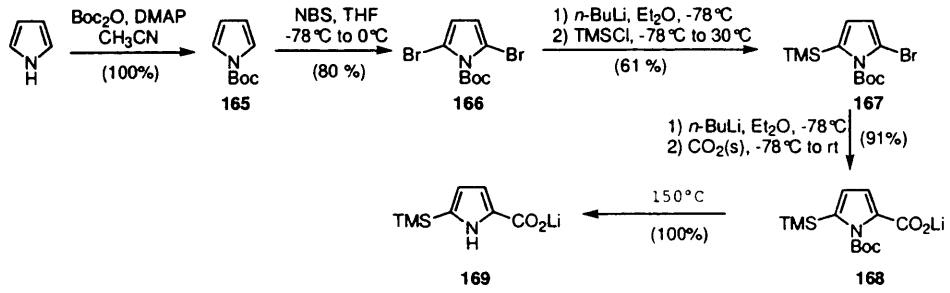
Preparation of *N*-Benzyl-*N*-methylcarbamoyl chloride (309)[81]



309

N-Benzylmethylamine (21.3 mL, 0.165 mL) was dissolved in freshly distilled diethyl ether under nitrogen, and the solution was cooled to 0°C. Redistilled *N,N*-diisopropylethylamine (Hünig's base) (37.5 mL, 0.215 mol) was added, followed by a dropwise addition of a phosgene solution in toluene (1.93 M, 120 mL, 0.231 mol). After 3 hours at 0°C, the solution was concentrated under vacuum to afford a thick yellow oil, which was triturated with diethyl ether (600 mL) for 10 minutes. The suspension was filtered, and the clear yellow filtrate was concentrated *in vacuo*. The residue was purified by SiO_2 flash chromatography (eluent: 5:95 to 1:9 AcOEt:Petrol) to give 23.1 g (76 %) of a colourless oil, which crystallised upon storage at 0°C. IR (neat) 1736 (s), 1495 (w), 1453 (m), 1419 (w), 1382 (m), 1245 (w), 1184 (w), 1076 (m), 1029 (w), 966 (w), 917 (w), 888 (w), 737 (w), 702 (m), 666 (w), 597 (w); ^{1}H-NMR (500 MHz, $CDCl_3$, 298 K) δ 7.36-7.29 (m, 3 H, arom.), 7.25-7.23 (m, 2 H, arom.), 4.69 and 4.55 (s, 2 H, $C\underline{H}_2$), 3.04 and 2.97 (s, 3 H, $C\underline{H}_3$); ^{13}C-NMR (125 MHz, $CDCl_3$, 298 K) δ 150.4 and 149.5 (C=O), 135.3 and 135.1 (arom.), 128.9 and 128.9 (arom.), 128.1 and 128.1 (arom.), 127.1 (arom.), 56.3 and 54.4 ($\underline{C}H_2$), 37.8 and 36.4 ($\underline{C}H_3$); HRMS Calcd for $C_9H_{11}NOCl$ $(M+H)^+$: *m/z* 184.0529126. Found: *m/z* 184.0525095.

Preparation of lithium 5-trimethylsilylpyrrole-2-carboxylate (169)[68]



***N-tert*-Butoxycarbonylpyrrole (165).**[71] Di-*tert*-butyl dicarbonate (66.4 g, 0.304 mol) was added to a solution of pyrrole (17.0 g, 0.253 mol) and DMAP (3.1 g, 0.0253 mol) in acetonitrile. The mixture was stirred at room temperature for 14 hours (open to the air). The solvent was then removed under vacuum, and the resulting dark oil was purified by fractional distillation through a Vigreux apparatus under high vacuum (b.p. 115°C / 28 mmHg) to afford 42.1 g (100 %) of a colourless oil. ^{1}H-NMR (500 MHz, $CDCl_3$, 298 K) δ 7.22 (dd, J = 2.4, 2.2 Hz, 2 H), 6.20 (dd, J = 2.5, 2.2 Hz, 2 H), 1.58 (s, 9 H); ^{13}C-NMR (125 MHz, $CDCl_3$, 298 K) δ 149.9, 119.9, 111.8, 83.5, 27.9.

***N-tert*-Butoxycarbonyl-2,5-dibromopyrrole (166).**[72] To a stirred solution of *N-tert*-butoxycarbonylpyrrole (30.0 g, 0.180 mol) in freshly distilled THF (360 mL) at –78°C under argon was added NBS (63.9 g, 0.359 mol). After the end of the addition, the cold bath was removed, and the reaction mixture was allowed to warm to 0°C, at which temperature the mixture was kept overnight (12 hours). Solid Na_2SO_3 was added, and the mixture was filtered. After concentration of the filtrate under vacuum, the residue was filtrerd on a silica pad, eluting with AcOEt:Petrol 1:4, to afford 46.6 g (80 %) of a pale yellow oil which was used immediately for the next step. ^{1}H-NMR (500 MHz, $CDCl_3$, 298 K) δ 6.22 (s, 2 H), 1.62 (s, 9 H); ^{13}C-NMR (125 MHz, $CDCl_3$, 298 K) δ 147.2, 116.2, 100.3, 86.4, 27.9.

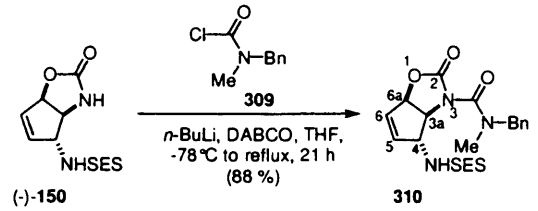
***N-tert*-Butoxycarbonyl-2-bromo-5-trimethylsilylpyrrole (167).**[68] *n*-BuLi (2.5 M solution in hexanes, 57.3 mL,0.143 mol) was added dropwise over 15 minutes under nitrogen to a stirred solution of the above dibromopyrrole (46.6 g, 0.143 mol) in freshly distilled diethyl ether (286 mL) at –78°C. After the end of the addition, the stirring was continued for 30 minutes at –78°C. Freshly distilled TMSCl (23.6 mL, 0.186 mol) was then added dropwise, and the cold bath was removed. The mixture was allowed to warm to –30°C, at which temperature was kept for 12

hours. The solvent was then removed under vacuum at room temperature. The residue was taken up in petroleum spirit (500 mL), and filtered. The filtrate was concentrated under vacuum to afford a dark brown oil, which was purified by flash chromatography (eluent: Petrol) to give 27.9 g (61 %) of a colourless oil. This unstable product was used immediately for the next step. ^{1}H-NMR (500 MHz, $CDCl_3$, 298 K) δ 6.37 (d, J = 3.4 Hz, 1 H), 6.28 (d, J = 3.4 Hz, 1 H), 1.62 (s, 9 H), 0.23 (s, 9 H); ^{13}C-NMR (125 MHz, $CDCl_3$, 298 K) δ 149.5, 138.8, 122.7, 117.4, 103.3, 85.1, 28.0, -0.3.

Lithium *N-tert*-Butoxycarbonyl-5-trimethylsilylpyrrole-2-carboxylate (168).[68] *n*-BuLi (2.5 M solution in hexanes, 33.7 mL, 0.0842 mol) was added dropwise over 15 minutes under nitrogen to a stirred solution of the above bromopyrrole (26.8 g, 0.0842 mol) in freshly distilled diethyl ether (280 mL) at –78 °C. After the end of the addition, the stirring was continued for 30 minutes at –78 °C. Solid CO_2 chunks were added while the mixture was allowed to rise to room temperature. The product was then extracted with water (3 x 150 mL). The combined aqueous layer was washed with light petroleum spirit (100 mL), and concentrated in vacuo to afford 22.1 g (91 %) of a white solid. ^{1}H-NMR (500 MHz, MeOD, 298 K) δ 6.36 (d, J = 3.2 Hz, 1 H), 6.27 (d, J = 3.2 Hz, 1 H), 1.57 (s, 9 H), 0.23 (s, 9 H); ^{13}C-NMR (125 MHz, MeOD, 298 K) δ 170.9, 152.5, 139.6, 136.8, 122.0,114.3, 84.8, 27.9, -0.3.

Lithium 5-trimethylsilylpyrrole-2-carboxylate (169).[68] The above solid *N*-Boc pyrrole (22.1 g, 0.0763 mol) derivative was heated neat at 150 °C for a total of 20 minutes by successively placing under high vacuum and then a stream of nitrogen (repeated several times) giving the deprotected title product (14.4 g, 100 %) as a white solid. IR (KBr) 2272 (br s), 1543 (s), 1459 (s), 1250 (s), 1219 (s), 1139 (m), 1043 (m), 987 (w), 950 (m), 841 (s), 781 (m), 508 (w); ^{1}H-NMR (500 MHz, MeOD, 298 K) δ 6.68 (d, J = 3.5 Hz, 1 H), 6.26 (d, J = 3.5 Hz, 1 H), 0.24 (s, 9 H); ^{13}C-NMR (125 MHz, MeOD, 298 K) δ 169.8, 134.3, 134.1, 118.4, 113.9, -0.9; HRMS Calcd for $C_8H_{12}LiNO_2SiNa$ $(M+Na)^+$: *m/z* 212.06950. Found: *m/z* 212.069347.

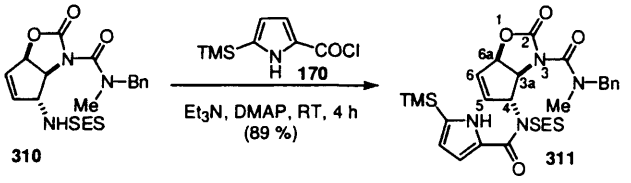
N-Acyl Oxazolidinone 310



To a stirred solution of (-)-**150** (3.0 g, 9.86 mmol) in dry THF (95 mL) at –78 °C under N_2 was added a solution of *n*-BuLi (6.2 mL, 1.6 M in hexanes, 9.92 mmol) dropwise over 5 min,

and 15 min later, carbamoyl chloride **309** (3.6 g, 19.7 mmol) in dry THF (5 mL) was added dropwise over 5 min. The cooling bath was removed, the reaction mixture was allowed to warm to RT over 15 min, and the reaction vessel was then transferred to an oil bath, where it was heated at reflux for 4 h. DABCO (6.6 g, 112.2. mmol) was then added in one portion and the heating at reflux was continued for 18 h. The reactants were then cooled to RT, and sat. aq. NH_4Cl (20 mL) and brine (30 mL) were added, and the organic layer was separated. The aqueous layer was then extracted with EtOAc (2 x 50 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was dissolved in the minimum amount of CH_2Cl_2 needed to fully solubilise it, and applied to a SiO_2 flash column packed with petrol. The product was then gradient eluted with 7:3 Petrol:EtOAc through to 1:1 Petrol:EtOAc to give **310** (4.2 g, 94%) as a white solid. M.p. 143°C; $[\alpha]_D$ –80.7 ° (*c* 0.5, MeOH); IR (KBr) 2954 (w), 1769 (s), 1685 (s), 1482 (w), 1453 (m), 1420 (w), 1403 (w), 1370 (s), 1324 (s), 1284 (m), 1254 (m), 1203 (s), 1167 (w), 1135 (s), 1111 (m), 1079 (s), 1042 (s), 1003 (w), 987 (w), 945 (w), 892 (m), 856 (s), 840 (s), 809 (m), 795 (m), 752 (m), 733 (s), 718 (w), 697 (s); ^{1}H-NMR (400 MHz, Tol-d_8, 323K) δ 7.12-6.90 (m, 5 H, Ph), 5.54 (dd, *J* = 5.7, 2.4 Hz, 1 H, H5), 5.40 (ddd, *J* = 5.7, 1.6, 1.6 Hz, 1 H, H6), 4.87 (br ddd, *J* = 7.3, 0.9 Hz, 1 H, H6a), 4.36 (d, *J* = 7.3 Hz, 1 H, H3a), 4.34 (d, *J* = 15.4 Hz, 1H, PhC<u>H</u>$_2$), 4.28 (d, *J* = 15.4 Hz, 1 H, PhC<u>H</u>$_2$), 4.26 (s, 1 H, H4), 3.98 (br s, 1 H, NH), 3.02 (m, 2 H, SES), 2.63 (s, 3 H, NMe), 1.01 (m, 2 H, SES), -0.06 (TMS); ^{13}C-NMR (125 MHz, Tol-d_8, 363 K, some resonances overlap and are hidden by the NMR solvent peaks) δ 154.2 (C=O), 152.3 (C=O), 137.2 (arom.), 136.7 (C5), 131.8 (C6), 128.1 (arom), 128.0 (arom.), 81.9 (C6a), 64.9 (C4), 64.4 (C3a), 54.0 (CH_2), 50.8 (SES), 36.0 (NMe), 11.3 (SES), -1.8 (TMS). HRMS Calcd. for $C_{20}H_{30}N_3O_5SSi$ $(M+H)^+$: *m/z* 452.1677. Found: *m/z* 452.16673.

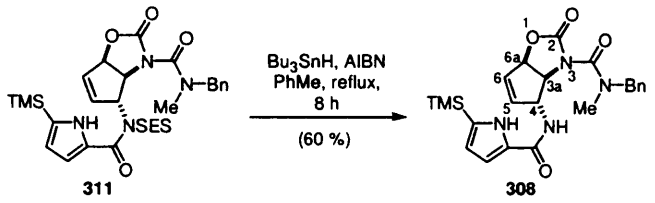
Pyrrole carboxamide 311



To a vigorously stirred suspension of the lithium carboxylate salt of 5-trimethylsilyl-pyrrole-2-carboxylic acid **169** (7.28 g, 38.5 mmol) in dry CH_2Cl_2 (77 mL) under an N_2 atmosphere was added oxalyl chloride (3.4 mL, 38.5 mL) in one portion followed by 4 drops of dry DMF. The reactants were stirred at RT for 2 h, and then taken up in a syringe, and added via syringe pump (flow rate 20 mL/h) to a solution of **310** (8.69 g, 19.2 mmol) in dry THF (116 mL) containing freshly distilled Et_3N (13.5 mL, 96.0 mmol) and 4-dimethylaminopyridine (235 mg, 1.92 mmol). When the addition of **170** was complete, sat. aq. $NaHCO_3$ (50 mL) was added. The mixture was then partitioned between brine (150 mL) and CH_2Cl_2 (300 mL). The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was

taken up in the minimum amount of CH_2Cl_2 needed to fully dissolve it, and applied to a SiO_2 flash column packed with petrol. The product was then eluted with a gradient 85:15 to 7:3 Petrol:EtOAc to give **311** (10.5 g, 89%) as a colourless oil. $[\alpha]_D$ −113 ° (*c* 0.4, MeOH); IR (NaCl neat film) 3335 (w), 2955 (w), 1777 (s), 1680 (s), 1537 (w), 1484 (w), 1452 (w), 1404 (w), 1351 (s), 1251 (s), 1173 (s), 1149 (s), 1054 (m), 952 (w), 918 (w), 842 (s), 803 (w), 757 (m), 700 (w), 631 (w); ^{1}H-NMR (400 MHz, C_6D_6, 343 K) δ 9.51 (br s, 1 H, NH pyrrole), 7.35 (dd, *J* = 3.8, 2.2 Hz, 1 H, pyrrole), 7.24-7.18 (m, 4 H, Ph), 7.06 (m, 1 H, Ph), 6.35 (dd, *J* = 3.8, 2.5 Hz, 1 H, pyrrole), 5.54 (ddd, *J* = 5.7, 1.8, 1.8 Hz, 1 H, H5), 5.51-5.43 (m, 3 H, H6 + H3a + H6a), 5.28 (m, 1 H, H4), 4.48 (d, *J* = 15.0 Hz, 1H, Ph$\underline{CH_2}$), and 4.40 (d, *J* = 15.5 Hz, 1 H, Ph$\underline{CH_2}$), 3.79-3.71 (m, 1 H, SES), 3.59-3.49 (m, 1 H, SES), 2.73 (s, 3 H, NMe), 1.27-1.17 (m, 2 H, SES), 0.05 (s, 9 H, TMS), -0.08 (s, 9 H, TMS); ^{13}C-NMR (100 MHz, C_6D_6, 343 K, some resonances overlap and are hidden by the NMR solvent peaks) δ 162.9 (C=O), 154.4 (C=O), 152.8 (C=O), 141.3 (C6), 137.1 (C5), 134.1 (arom), 133.1 (alkene), 130.6 (pyrrole), 129.0 (arom.), 121.7 (pyrrole), 119.6 (pyrrole), 83.4 (C6a), 70.9 (C4), 62.2 (C3a), 53.7 (CH_2), 52.0 (SES), 35.7 (NMe), 10.6 (SES), -1.6 (TMS), -2.1 (TMS). HRMS Calcd. for $C_{28}H_{40}N_4O_6SSi_2Na$ $(M+Na)^+$: *m/z* 639.2114. Found: *m/z* 639.21130.

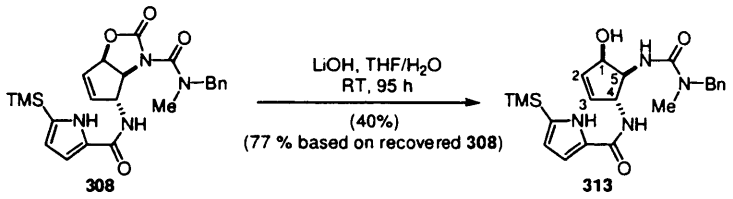
Pyrrole carboxamide 308



To a degassed solution of the sulfonamide **311** (5.00 g, 8.11 mmol) in freshly distilled toluene (42 mL) under N_2 was added Bu_3SnH (3.4 mL, 12.6 mmol) and the mixture was brought to reflux. AIBN (4.40 g, 26.7 mmol) was then added in 32 equal portions [137 mg, (0.1 equiv)] approx. every 15 min over 8 h. The mixture was allowed to cool to RT, and the solvent was removed *in vacuo*. The organotin by-products were removed by gradient elution SiO_2 flash chromatography with 9:1 to 8:2 Petrol/EtOAc. The product **308** (2.20 g, 60%) eluted with 7:3 Petrol/EtOAc and was obtained as a yellow oil. $[\alpha]_D$ −289 ° (*c* 1, MeOH); IR (KBr) 2956 (m), 2362 (w), 1779 (s), 1696 (s), 1621 (m), 1577 (m), 1549 (w), 1521 (m), 1481 (w), 1455 (m), 1401 (w), 1354 (s), 1251 (m), 1194 (s), 1147 (w), 1051 (s), 992 (w), 960 (w), 842 (s), 800 (m), 760 (m); ^{1}H-NMR (500 MHz, $CDCl_3$, 328 K) δ 9.19 (br s, 1 H, NH pyrrole), 7.34-7.24 (m, 5 H, Ph), 6.54 (dd, *J* = 3.5, 2.4 Hz, 1 H, pyrrole), 6.35 (dd, *J* = 3.3, 3.0 Hz, 1 H, pyrrole), 6.13 (d, *J* = 7.3 Hz, 1 H, NHCO of urea), 6.07 (br s, 2 H, H5 + H6), 5.65 (d, *J* = 7.5 Hz, 1 H, H6a), 4.89 (apparent d, *J* = 7.3 Hz, 1H, H3a), 4.73 (d, *J* = 15.3 Hz, 1 H, $\underline{CH_2}$Ph), 4.51 (d, *J* = 15.3 Hz, 1H, $\underline{CH_2}$Ph), 2.96 (s, 3 H, NMe), 0.25 (s, 9 H, TMS); ^{13}C-NMR (125 MHz, $CDCl_3$, 328 K) δ 160.8 (C=O), 153.6 (C=O), 153.0 (C=O), 136.5 (arom.), 136.4 (arom.), 136.1 (alkene), 131.7 (alkene),

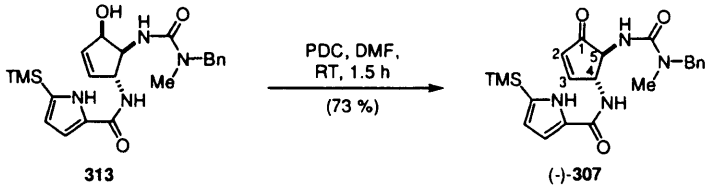
128.8 (arom.), 128.7 (arom.), 127.8 (arom.), 127.6 (arom.), 118.4 (pyrrole), 110.1 (pyrrole), 82.8 (C6a), 63.8 (C3a), 61.7 (C4), 53.7 (CH_2), 36.1 (NMe), -1.2 (TMS). HRMS Calcd. for $C_{23}H_{29}N_4O_4Si$ $(M+H)^+$: *m/z* 453.19592. Found: *m/z* 453.19528.

Cyclopentenol 313



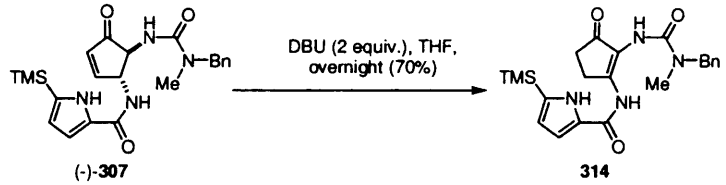
To a vigorously stirred solution of oxazolidinone **308** (3.55 g, 7.84 mmol) in THF:H_2O (9:1) (100 mL) at RT was added LiOH.H_2O (3.29 g, 78.5 mmol) in one portion, and the solution stirred at RT for 128 h. The solvents were then removed *in vacuo*, and the residue was partitioned between EtOAc (100 mL) and H_2O (100 mL). The layers were separated, and the aqueous layer was further extracted with EtOAc (2 x 100 mL). The combined organic layer was washed with H_2O (50 mL), sat. aq. NH_4Cl (50 mL), brine (50 mL), and dried over $MgSO_4$; it was then filtered and concentrated *in vacuo*. The residue was then purified by SiO_2 flash chromatography using EtOAc as eluent to give **313** (1.32 g, 40%) as a white foam, as well as some recovered **308** (1.72 g, yield of the reaction based upon recovered **308** = 77 %). $[\alpha]_D$ – 204.1 ° (*c* 1, MeOH); IR (neat) 3312 (m), 2956 (w), 1633 (s), 1555 (m), 1527 (s), 1453 (w), 1389 (w), 1339 (w), 1250 (m), 1203 (m), 1148 (w), 1049 (w), 950 (w), 841 (m), 758 (w), 699 (w); ^{1}H-NMR (500 MHz, $CDCl_3$, 298 K) δ 9.51 (br s, 1H, pyrrole NH), 7.50 (d, *J* = 5.9 Hz, 1 H, pyrrole CONH), 7.31-7.20 (m, 5 H, Ph), 6.83 (dd, *J* = 3.6, 2.3 Hz, 1 H, pyrrole), 6.41 (dd, *J* = 3.6, 2.6 Hz, 1 H, pyrrole), 6.18 (dd, *J* = 6.1, 1.4 Hz, H3), 6.07 (ddd, *J* = 5.1, 2.4, 2.4 Hz, 1 H, H2), 5.87 (d, *J* = 7.0 Hz, urea NH), 5.08 (m, 1 H, H4), 4.66 (br s, 1 H, H1), 4.51 (d, *J* = 15.9 Hz, $\underline{CH_2}$Ph), 4.47 (d, *J* = 15.9 Hz, 1H, $\underline{CH_2}$Ph), 4.19 (dd, *J* = 13.2, 7.1 Hz, 1 H, H5), 3.58 (br s, 1 H, OH), 2.84 (s, 3 H, NMe), 0.30 (s, 9 H, TMS); ^{13}C-NMR (125 MHz, $CDCl_3$, 298 K) δ 162.3 (C=O), 159.0 (C=O), 137.6 (arom.), 137.2 (C3), 135.8 (arom.), 133.1 (C2), 129.2 (arom.), 128.6 (arom.), 127.4 (arom.) 127.2 (arom.), 118.5 (pyrrole), 111.1 (pyrrole), 96.1 (pyrrole C with Me_3Si), 73.2 (C1), 60.0 (C4), 59.9 (C5), 52.2 (CH_2), 34.0 (NMe), -1.1 (TMS). HRMS Calcd. for $C_{22}H_{31}N_4O_3Si$: $(M+H)^+$: *m/z* 427.2167. Found: *m/z* 427.21697.

Cyclopentenone 307



To a stirred solution of alcohol **313** (1.32 g, 3.10 mmol) in DMF (31 mL) was added pyridinium dichromate (5.82 g, 15.5 mmol) and the mixture was stirred at RT for 2 h. The mixture was then partitioned between EtOAc (500 mL) and H_2O (100 mL), and the organic layer was separated and washed successively with H_2O (6 x 50 mL) and brine (50 mL). After being dried over $MgSO_4$, the organic fraction was filtered and the solvent was removed *in vacuo*. The residue was then purified by SiO_2 flash chromatography using EtOAc to give **307** (0.95 g, 73%) as a colorless oil. $[\alpha]_D$ –242 ° (*c* 1, MeOH); IR (NaCl neat film) 2956 (m), 1725 (s), 1835 (s), 1553 (s), 1535 (s), 1452 (w), 1388 (w), 1335 (m), 1250 (m), 1199 (m), 1148 (w), 1117 (w), 1080 (w), 1049 (w), 979 (w), 842 (s), 798 (w), 759 (m), 699 (w); ^{1}H-NMR (500 MHz, $CDCl_3$, 298 K) δ 9.33 (br s, 1 H, NH pyrrole), 7.88 (d, *J* = 6.0 Hz, 1 H, H3), 7.76 (m, 1 H, pyrrole CONH), 7.31-7.18 (m, 5 H, Ph), 6.77 (dd, *J* = 3.3, 2.4 Hz, 1 H, pyrrole), 6.38 (dd, *J* = 3.4, 2.7 Hz, 1 H, pyrrole), 6.29 (d, *J* = 6.1 Hz, 1 H, H2), 5.32 (d, *J* = 4.4 Hz, 1 H, urea NH), 4.71 (br s, 1 H, H4), 4.54 (d, *J* = 15.8 Hz, 1H, $\underline{CH_2}$Ph, 4.41 (d, *J* = 15.8 Hz, $\underline{CH_2}$Ph), 4.37 (dd, *J* = 4.3, 4.3 Hz, 1 H, H5), 2.87 (s, 3 H, NMe), 0.24 (s, 9 H, TMS); ^{13}C-NMR (125 MHz, $CDCl_3$, 298 K) δ 201.3 (C=O ketone), 162.3 (C=O), 160.7 (C3), 158.9 (C=O), 137.1 (arom.), 136.1 (arom.), 131.4 (C2), 128.9 (arom.), 128.8 (arom.), 127.5 (arom.), 127.3 (arom.), 118.5 (pyrrole), 111.1 (pyrrole.), 62.7 (C5), 59.2 (C4), 52.3 (CH_2), 34.3 (NMe), -1.1 (TMS). HRMS Calcd. for $C_{22}H_{29}N_4O_3Si$ $(M+H)^+$: *m/z* 425.2011. Found: *m/z* 425.20174.

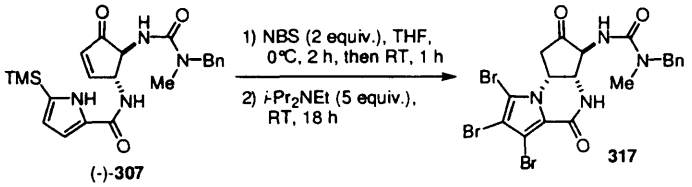
Rearranged Enone 314



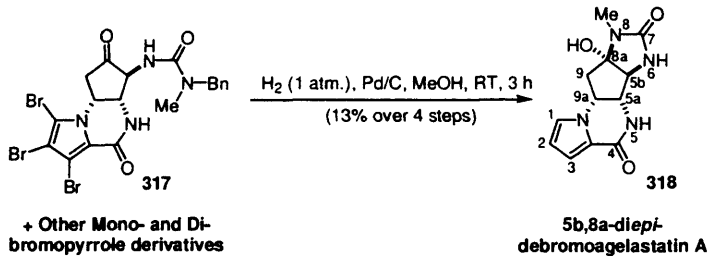
To a solution of enone **307** (21.0 mg, 49.6 µmol) in dry THF (5 mL) was added DBU (100 µl of a stock solution in THF, 49.6 µmol) under nitrogen, and the mixture was stirred at room temperature. After 2.5 h, more DBU (100 µL of the stock solution in THF, 49.6 µmol) was added, and the mixture was stirred overnight. After 15.5 h, sat. aq. NH_4Cl (5 mL) was added, and the solution was partitioned between brine (5 mL) and AcOEt (30 mL). The layers were separated, and the organic layers was dried (MgSO4). After concentration under vacuum, the residue was loaded onto a preparative TLC plate (eluent : AcOEt/Petrol 1:1) to give **314** (14 mg, 70%) as an oil. IR (neat) 3295 (w), 2959 (w), 1670 (m), 1822 (s), 1530 (s), 1501 (s), 1452 (w), 1392 (w), 1358 (m), 1297 (m), 1250 (w), 1220 (w), 1156 (s), 969 (w), 841 (s), 756 (w), 699 (w) ; ^{1}H-NMR (500 MHz, $CDCl_3$, 298 K) δ 12.69 (s, 1 H, N$\underline{H}$CO pyrrole), 9.20 (s, 1 H, N$\underline{H}$ pyrrole), 7.36-7.24 (m, 5 H, arom.), 7.06 (dd, *J* = 3.7, 2.3 Hz, 1 H, pyrrole), 6.77 (s, 1 H, N$\underline{H}$CO urea), 6.45 (dd, *J* = 3.6, 2.7 Hz, 1 H, pyrrole.), 4.61 (s, 2 H, $C\underline{H_2}$ benzyl), 3.35 (m, 2 H, CH_2), 3.02 (s, 3

H, NC<u>H</u>$_3$), 2.50 (m, 2 H, C<u>H</u>$_2$), 1.50 (s, 9 H, Boc), 0.26 (s, 9 H, TMS); ^{13}C-NMR (125 MHz, $CDCl_3$, 298 K) δ 199.1 (C=O), 158.6 (C=O), 155.7 (C=O), 149.1 (alkene), 137.9 (alkene), 136.8 (arom.), 129.6 (arom.), 128.9 (arom.), 127.8 (pyrrole), 127.6 (arom.), 118.9 (pyrrole), 118.6 (pyrrole), 112.9 (pyrrole), 52.7 (<u>C</u>H$_2$ benzyl), 35.0 (NC<u>H</u>$_3$), 31.8 (alkene), 25.4 (alkene), -1.2 (TMS). HRMS Calcd for $C_{22}H_{28}N_4O_3Si$ $(M)^+$: *m/z* 424.19306 Found: *m/z* 424.19447.

Tricyclic Pyrrolocyclopentanone 212 and di*epi*-debromoagelastatin A 318 *via* 317

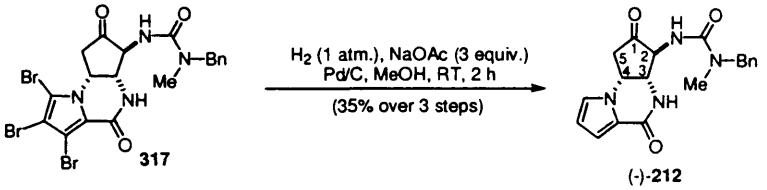


To a solution of the α,β-unsaturated ketone **307** (680 mg, 1.61 mmol) in dry THF (16 mL) at 0 °C was added *N*-bromosuccinimide (NBS) (572 mg, 3.21 mmol) in one portion. The mixture was stirred for 2 h at 0 °C and then at RT for 1 h. To the reaction mixture was then added Hünig's base (1.4 mL, 8.03 mmol) dropwise, and the stirring continued overnight (18 h). Sat. aq. NH_4Cl (20 mL) was then added, and the solution was multiply extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (10 mL) and dried over $MgSO_4$. After filtration and removal of the solvents *in vacuo* a residue was obtained that was used directly for the next step; the residue was a mixture of components that contained **317** as the major product, along with other di- and mono-bromopyrroles.



To a solution of the above product mixture containing **317** (150 mg, *ca.* 0.294 mmol) in methanol (3 mL) was added Pd/C (10% wet, 62 mg, 0.0294 mmol), and the mixture was hydrogenated under a atmosphere of H_2 (1 atm.) at RT for 3 h. The mixture was then diluted with MeOH (15 mL) and filtered on a Celite pad. After concentration *in vacuo*, the residue was purified by SiO_2 flash chromatography (AcOEt/ MeOH 9:1 then 8:2) to afford **318** (17 mg, 13% combined yield over 4 steps) as a white solid. IR (KBr) 3260 (br s), 1680 (s), 1649 (s), 1555 (m),

1474 (m), 1404 (w), 1369 (w), 1333 (m), 1210 (m), 752 (m); ^{1}H-NMR (500 MHz, MeOD, 298 K) δ 7.10 (dd, *J* = 2.5, 1.6 Hz, 1 H, H1), 6.84 (dd, *J* = 3.9, 1.5 Hz, 1 H, H3), 6.22 (dd, *J* = 3.9, 2.7 Hz, 1 H, H2), 4.68 (dd, J = 5.3, 4.7 Hz, 1 H, H9a), 4.30 (dd, *J* = 7.3, 5.6 Hz, 1 H, H5a), 4.09 (d, *J* = 7.3 Hz, 1 H, H5b), 3.00 (dd, *J* = 15.2, 1.5 Hz, 1 H, H9), 2.51 (s, 3 H, NC<u>H</u>$_3$), 2.39 (dd, *J* = 15.2, 5.1 Hz, 1 H, H9); ^{13}C-NMR (125 MHz, MeOD, 298 K) δ 163.1 (C=0), 161.3 (C=O), 124.2 (C1), 123.7 (C3), 115.6 (C2), 111.6 (C3a), 100.8 (C8a), 59.0 (C5b), 57.8 (C5a), 56.2 (C9a), 38.5 (C9), 23.8 (N<u>C</u>H$_3$).

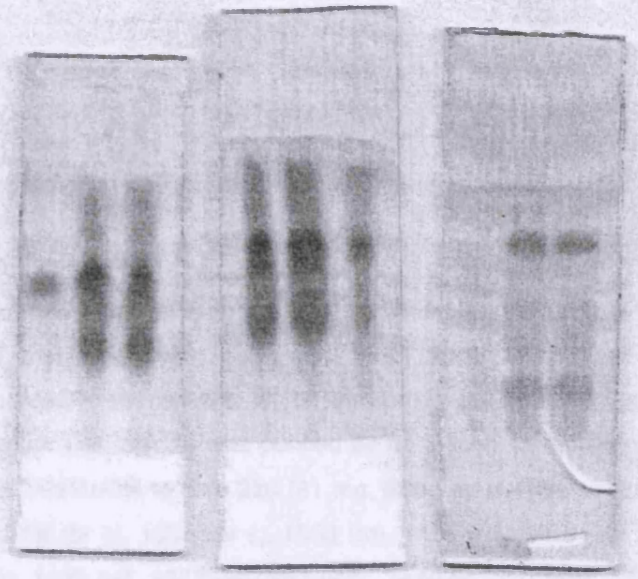


+ Other Mono- and Di-bromopyrrole derivatives

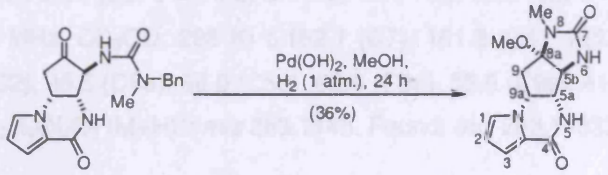
A solution of the above product mixture containing **317** was dissolved in MeOH (16 mL) and solid NaOAc (396 mg, 4.83 mmol) was added followed by 10% Pd on C (wet) (339 mg, *ca.* 0.161 mmol). The mixture was hydrogenated under an atmosphere of H_2 at 1 atm for 2 h. The suspension was then filtered through Celite, and the filtrate concentrated *in vacuo*. The residue was taken up in EtOAc (50 mL), washed with H_2O (5 mL) and brine (5 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the residue by SiO_2 flash chromatography using EtOAc:MeOH 95:5 afforded **212** (195 mg, 35% over 3 steps) as a colorless oil. $[\alpha]_D$ –79.3 ° (*c* 0.3, MeOH); IR (NaCl neat film) 3320 (s), 2922 (m), 1756 (s), 1665 (s), 1533 (s), 1470 (m), 1420 (m), 1391 (m), 1358 (m), 1317 (m), 1267 (m), 1235 (m), 1199 (m), 1139 (m), 1065 (m), 910 (s), 731 (s), 648 (m); ^{1}H-NMR (500 MHz, $CDCl_3$, 298 K) δ 7.72 (br s, 1 H, pyrrole CONH), 7.30-7.15 (m, 5 H, arom.), 6.86 (dd, *J* = 3.8, 1.4 Hz, 1 H, pyrrole), 6.78 (dd, *J* = 2.5, 1.6 Hz, 1 H, pyrrole), 6.25 (dd, *J* = 3.8, 2.7 Hz, 1 H, pyrrole), 6.10 (d, *J* = 5.8 Hz, 1 H, CONH urea), 4.84 (dd, *J* = 5.7, 5.7 Hz, 1 H, H4), 4.55 (m, 1 H, H3), 4.47 (d, *J* = 16.0 Hz, 1 H, -C<u>H</u>$_2$Ph), 4.30 (d, *J* = 16.0 Hz, 1 H, -C<u>H</u>$_2$Ph), 3.59 (m, 1 H, H2), 3.16 (dd, *J* = 18.8, 6.1 Hz, 1 H, H5), 3.01 (d, *J* = 18.8, 1 H, H5), 2.77 (s, 3 H, N-C<u>H</u>$_3$); ^{13}C-NMR (125 MHz, $CDCl_3$ 298 K) δ 207.5 (C=O ketone), 159.9 (C=0), 157.7 (C=O), 137.0 (arom.), 128.7 (arom.), 127.4 and 127.1 (arom.), 123.4 (pyrrole), 122.8 (pyrrole), 115.2 (pyrrole), 111.2 (pyrrole), 62.3 (C2), 55.8 (C3), 52.1 (<u>C</u>H$_2$), 50.6 (C4), 42.3 (C5), 34.2 (N-<u>C</u>H$_3$); HRMS Calcd. for $C_{19}H_{21}N_4O_3$ $(M+H)^+$: *m/z* 353.16136. Found: *m/z* 353.16339.

TLC picture at the end of each step in this one-pot reaction sequence (anisaldehyde stain):

NBS Step Hunig's Cyclisation Hydrogenation



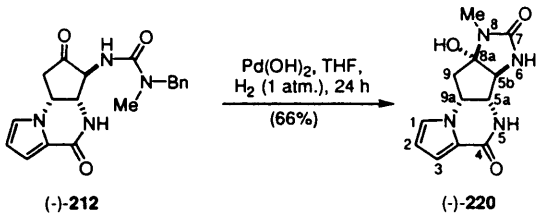
(-)-8a-*O*-Methyldebromoagelastatin A



(-)-**212** **319**

To a solution of (-)-**212** (12 mg, 34.1 µmol) in MeOH (2 mL) was added 20% $Pd(OH)_2$ on carbon (7 mg). The mixture was hydrogenated under a atmosphere of H_2 (1 atm) for 15 h at RT, then loaded onto a thin-layer chromatography plate (1 mm thick). The product was eluted twice with a 82:18 mixture of AcOEt/MeOH to give **319** (3.2 mg, 36%) as a white solid. ^{1}H-NMR (500 MHz, CD3OD, 298 K) δ 7.03 (dd, *J* = 2.5, 1.6 Hz, 1 H, H1), 6.88 (dd, *J* = 3.9, 1.5 Hz, 1 H, H3), 6.23 (dd, *J* = 3.9, 2.5 Hz, 1 H, H2), 4.65 (d(app)t, *J* = 11.6, 6.0 Hz, 1 H, H9a), 4.00 (dd, *J* = 5.4, 2.1 Hz, 1 H, H5a), 3.96 (d, *J* = 2.1 Hz, 1 H, H5b), 3.09 (s, 3 H, OMe), 2.76 (s, 1 H, NMe), 2.62 (dd, *J* = 13.6, 6.3 Hz, 1 H, H9), 2.36 (dd, *J* = 13.6, 9.4 Hz, 1 H, H9); ^{13}C-NMR (125 MHz, CD_3OD, 298 K) δ 162.9, 161.7, 125.6, 123.0, 115.5, 111.2, 100.2, 68.0, 62.9, 61.8, 55.1, 50.4 40.9, 24.6.

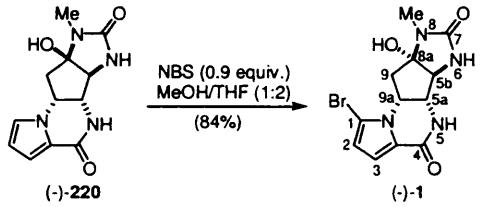
(-)-Debromoagelastatin A (220)



(-)-**212** (-)-**220**

To a solution of **212** (165 mg, 0.468 mmol) in freshly distilled THF (4.7 mL) was added 20% $Pd(OH)_2$ on carbon (65 mg). The mixture was hydrogenated under a atmosphere of H_2 (1 atm) for 23 h at RT, then diluted with methanol (20 mL) and filtered through Celite. The filter pad was washed with MeOH to remove all of the products, and the combined filtrate was concentrated *in vacuo*. The residue was purified by SiO_2 flash chromatography, eluting with an 85:15 mixture of EtOAc/MeOH to give **220** (81 mg, 66%) as a white solid. $[\alpha]_D$ –64.8 ° (*c* 0.48, MeOH); IR (KBr) 3286 (br s), 1652 (br s), 1553 (m), 1474 (m), 1419 (m), 1377 (m), 1302 (m), 1266 (w), 1210 (w), 1133 (w), 1072 (w), 753 (w); ^{1}H-NMR (500 MHz, CD_3OD, 298 K) δ 7.02 (dd, *J* = 2.6, 1.6 Hz, 1 H, H1), 6.88 (dd, *J* = 3.9, 1.6 Hz, 1 H, H3), 6.22 (dd, *J* = 3.9, 2.6 Hz, 1 H, H2), 4.65 (apparent dt, *J* = 9.7, 6.1 Hz, 1 H, H9a), 4.00 (d, *J* = 5.4 Hz, 1 H, H5a), 3.80 (s, 1 H, H5b), 2.79 (3H, NMe), 2.61 (dd, *J* = 13.3, 6.4 Hz, 1 H, H9), 2.27 (dd, *J* = 13.3, 10.3 Hz, 1 H, H9); ^{13}C-NMR (125 MHz, CD_3OD, 298 K) δ 162.1 (C7), 161.3 (C4), 125.6 (C1), 122.9 (C3a), 115.4 (C3), 111.1 (C2), 95.8 (C8a), 68.0 (C5b), 62.9 (C5a), 55.6 (C9a), 41.6 (C9), 24.2 (N-Me). HRMS Calcd. for $C_{12}H_{15}N_4O_3$ $(M+H)^+$: *m/z* 263.1145. Found: *m/z* 263.11333.

(-)-Agelastatin A



(-)-**220** (-)-**1**

To a stirred solution of **220** (69 mg, 0.263 mmol) in MeOH (5 mL) and freshly distilled THF (10 mL) at 0°C was added recrystallised *N*-bromosuccinimide (NBS) (23.4 mg, 0.132 mmol). The cold bath was removed immediately after the addition, and the reaction mixture was allowed to warm to RT with stirring. After 2 h, a sample of the reaction mixture was concentrated and analyzed by ^{1}H NMR; this showed a 56% conversion of (-)-debromoagelastatin A (**220**) to (-)-agelastatin A (**1**). The mixture was recooled to 0°C, and more NBS (18.4 mg, 0.103 mmol) was added. The ice bath was removed and the reactants were stirred for a further 2 h at RT.

The solution was then concentrated *in vacuo*, and the residue was purified by SiO_2 flash chromatography, eluting with 8:2 EtOAc/MeOH, to give (-)-agelastatin A (75.4 mg, 84%) as a white solid. $[\alpha]_D$ –84.2 ° (*c* 1, MeOH); IR (KBr) 3280 (m), 1652 (s), 1554 (m), 1424 (s), 1377 (m), 1304 (w), 1269 (w), 1196 (w), 1139 (w), 1091 (w), 935 (w), 749 (w), 663 (w) ; ^{1}H-NMR (500 MHz, CD_3OD, 298 K) δ 6.90 (d, *J* = 4.1 Hz, 1 H, H3), 6.31 (d, *J* = 4.1 Hz, 1 H, H2), 4.58 (m, 1 H, H9a), 4.07 (d, *J* = 5.5 Hz, 1 H, H5a), 3.88 (s, 1 H, H5b), 2.80 (s, 3 H, N-Me), 2.63 (dd, *J* = 13.0, 6.5 Hz, 1 H, H9), 2.09 (dd, *J* = 12.6, 12.6 Hz, 1 H, H9); ^{13}C-NMR (125 MHz, CD_3OD, 298 K) δ 161.4 (C7), 161.1 (C4), 124.1 (C3a), 116.0 (C3), 113.8 (C2), 107.2 (C1), 95.6 (C8a), 67.4 (C5b), 62.2 (C5a), 54.3 (C9a), 40.0 (C9), 24.2 (N-Me). HRMS: Calcd. for $C_{12}H_{14}N_4O_3{}^{79}Br$ $(M+H)^+$: *m/z* 341.0251. Found: *m/z* 341.0251.

References

1 Newman, D.J.; Cragg, G.M. ; Snader, K.M. *J. Nat. Prod.* **2003**, *66*, 1022-1037.
2 D'Ambrosio, M.; Guerriero, A.; Debitus, C.; Ribes, O.; Pusset, J.; Leroy, S.; Pietra, F. *J. Chem. Soc., Chem. Commun.* **1993**, 1305-1306.
3 D'Ambrosio, M.; Guerriero, A.; Chiasera, G.; Pietra, F. *Helv. Chim. Acta* **1994**, *79*, 1895-1902.
4 Hong, T.W. ; Jímenez, D.R. ; Molinski, T.F. *J. Nat. Prod.* **1998**, *61*, 158-161.
5 D'Ambrosio, M. ; Guerriero, A. ; Ripamonti, M. ; Debitus, C. ; Waikedre, J., Pietra, F. *Helv. Chim. Acta* **1996**, *79*, 727-735.
6 Assmann, M. ; Lichte, E. ; Pawlik, J.R. ; Köck, M. *Mar. Ecol. Prog. Ser.* **2000**, *207*, 255-262.
7 Forenza, S. ; Minale, L. ; Riccio, R. ; Fattorusso, E. *Chem. Commun.* **1971**, 1129-1130.
8 Garcia, E. E. ; Benjamin, L. E. ; Fryer, R. I. *J. Chem. Commun.* **1973**, 78-79.
9 Andrade, P. ; Willoughby, S.A. ; Pomponi, R.G. ; Kerr, R.G. *Tetrahedron Lett.* **1999**, *40*, 4775-4778.
10 Cafieri, F. ; Fattorusso, E. ; Mangoni, A. ; Taglialatela-Scafati, O. *Tetrahedron* **1996**, *52*, 13713-13720.
11 Cafieri, F. ; Fattorusso, E. ; Taglialatela-Scafati, O. *J. Nat. Prod.* **1998**, *61*, 122-125.
12 Kitagawa, I. ; Kobayashi, M. ; Kitanaka, I. ; Kido, M. ; Kyogoku, Y. *Chem. Pharm. Bull.* **1983**, *31*, 2321-2328.
13 Assmann, M. ; Lichte, E. ; van Soest, R.W.M. ; Köck, M. *Org Lett.* **1999**, *1*, 455-457.
14 Lindel, T. ; Hochgürtel, M. ; Assmann, M. ; Köck, M. *J. Nat. Prod.* **2000**, *63*, 1566-1569.
15 Al Mourabit, A. ; Potier, P. *Eur. J. Org. Chem.* **2001**, 237-243.
16 Faulkner, D. J. *Nat. Prod. Rep.* **2001**, *18*, 1-49.
17 Sharma, G.M. ; Burkholder, P.R. *Lloydia* **1969**, *32*, 466-483.
18 Sharma, G.M. ; Burkholder, P.R. *Chem. Commun.* **1971**, 151-152.
19 Sharma, G. ; Magdoff-Fairchild, B. *J. Org. Chem.* **1977**, *42*, 4118-4124.
20 De Nanteuil, G. ; Ahond, G. ; Guilhem, J. ; Poupat, C. ; Tran Huu Dau, E. ; Potier, P. ; Pusset, M. ; Pusset, J. ; Laboute, P. *Tetrahedron* **1985**, *41*, 6019-6033.
21 Foley, L.H. ; Büchi, G. *J. Am. Chem. Soc.* **1982**, *104*, 1776-1777.
22 Wiese, K.J. ; Yakushijin, K. ; Horne, D.A. *Tetrahedron Lett.* **2002**, 5135-5136.
23 Sharma, G.M. ; Buyer, J.S. ; Pomerantz, M.W. *J. Chem. Soc., Chem. Commun.* **1980**, 435-436.
24 Cimino, G. ; De Rosa, S. ; De Stefano, S. ; Mazzarella, L. ; Puliti, R. ; Sodano, G. *Tetrahedron Lett.* **1982**, *23*, 767-768.
25 Pettit, G. ; Herald, C.L. ; Leet, J.E. ; Gupta, R. ; Schaufelberger, D.E. ; Bates, R.B. ; Clewlow, P.J. ; Doubek, D.L. ; Manfredi, K.P. ; Rützler, K. ; Schmidt, J.M. ; Tackett, L.P. ; Ward, F.B. ; Bruck, M. ; Camou, F. *Can. J. Chem.* **1990**, *68*, 1621-1624.
26 Curman, D. ; Cinel, B. ; Williams, D.E. ; Rundle, N. ; Block, W.D. ; Goodarzi, A.A. ; Hutchins, J.R. ; Clarke, P.R. ; Zhou, B.-B. ; Lees-Miller, S.P. ; Andersen, R.J. ; Roberge, M. *J. Biol. Chem.* **2001**, *276*, 17914-17919.
27 Tasdemir, D. ; Mallon, R. ; Greenstein, M. ; Feldberg, L.R. ; Kim, S.C. ; Collins, K. ; Wojciechowicz, D. ; Mangalindan, G.C. ; Concepción, G.P. ; Harper, M.K. ; Ireland, C.M. *J. Med. Chem.* **2002**, *45*, 529-532.
28 Kolsch, W. *Biochem. J.* **2000**, *351*, 289-305.
29 Sharma, V.; Lansdell, T.A.; Jin, G.; Tepe, J.J. *J. Med. Chem.* **2004**, *47*, 3700-3703.
30 Moreland, L.W. *Rheumatol.* **1999**, *26* (Suppl. 57), 7-15.
31 Breton, J.J. ; Chabot-Fletcher, M.C. *J. Pharmacol. Exp. Therap.* **1997**, *282*, 459-466.
32 Meijer, L. ; Thunnissen, A.-M.W.H.; White, A.W.; Garnier, M.; Nikolic, M.; Tsai, L.-H. ; Walter, J. ; Cleverley, K.E. ; Salinas, P.C. ; Wu, Y.-Z. ; Biernat J. ; Mandelkow, E.-M. ; Kim, S.-H. ; Pettit, G.R. *Chem. Biol.* **2000**, *7*, 51-63.
33 Kobayashi, J. ; Ohizumi, Y. ; Nakamura, H. ; Hirata, K. ; Wakamatsu, K. ; Miyazawa, T. *Experientia* **1986**, *42*, 1064-1065.
34 Kobayashi, J. ; Nakamura, H. ;Ohizumi, Y. *Experientia* **1988**, *44*, 86-87.
35 Albizati, K.F. ; Faulkner, D.J. *J. Org. Chem.* **1985**, *50*, 4163-4164.
36 Linington, R.G. ; Williams, D.E. ; Tahir, A. ; Van Soest, R. ; Andersen, R.J. *Org. Lett.* **2003**, *5*, 2735-2738.
37 Barrios Sosa, A.C. ; Yakushijin, K. ; Horne, D.A. *Tetrahedron Lett.* **2000**, *41*, 4295-4299.

38 Cafieri, F. ; Fattorusso, E. ; Mangoni, A. ; Taglialatela-Scafati, O. *Tetrahedron Lett.* **1995**, *43*, 7893-7896.
39 Xu, Y. ; Yakushijin, K. ; Horne, D.A. *J. Org. Chem.* **1997**, *62*, 456-464.
40 Anderson, H. J. ; Lee, S.-F. *Can. J. Chem* **1965**, *43*, 409-414.
41 Annoura, H. ; Tatsuoka, T. *Tetrahedron Lett.* **1995**, *36*, 413-416.
42 Pettit, G.R. ; McNulty, J. ; Delbert, L.H. ; Doubek, D.L. ; Chapuis, J.-C. ; Schmidt, J.M. ; Tackett, L.P. ; Boyd, M.R. *J. Nat. Prod.* **1997**, *60*, 180-183.
43 Jacquot, D.E. ; Hofmann, H. ; Polborn, K. ; Lindel, T. *Tetrahedron Lett.* **2002**, *43*, 3699-3702
44 Poullennec, K.G. ; Romo, D. *J. Am. Chem. Soc.* **2003**, *125*, 6344-6345.
45 Poullennec, K.G. ; Kelly, A.T. ; Romo, D. *Org. Lett.* **2002**, *4*, 2645-2648.
46 Chung, R. ; Yu, E. ; Incarvito, C.D.; Austin, D.J. *Org. Lett.* **2004**, *6*, 3881-3884.
47 Kinnel, R.B., Gehrken, H.-P. ; Scheuer, P.J. *J. Am. Chem. Soc.* **1993**, *115*, 3376-3377.
48 Kato, T. ; Shiruzi, Y. ; Izumida, H. ; Yokoyama, A. ; Endo, M. *Tetrahedron Lett.* **1995**, *36*, 2133-2136.
49 Bélanger, G. ; Hong, F.-T. ; Overman, L.E. ; Rogers, B.N. ; Tellew, J.E. ; Trenkle, W.C. *J. Org. Chem.* **2002**, *67*, 7880-7160.
50 Overman, L.E. ; Rogers, B.N. ; Tellew, J.E. ; Trenkle, W.C. *J. Am. Chem. Soc.* **1997**, *119*, 7159-7160.
51 Starr, J.T. ; Koch, G. ; Carreira, E.M. *J. Am. Chem. Soc.* **2002**, *122*, 8793-8794.
52 Lovely, , C.J. ; Du, H. ; Dias, H.V.R. *Org. Lett.* **2001**, *3*, 1319-1322.
53 Koenig, S.G. ; Miller, S.M. ; Leonard, K.A. ; Löwe, R.S. ; Chen, B.C. ; Austin, D.J. *Org. Lett.* **2003**, *5*, 2203-2206.
54 Romo, D. ; Dilley, A.S. *Org. Lett.* **2001**, *3*, 1535-1538.
55 Kinnel, R. B. ; Gehrken, H.-P. ; Swali, R. ; Skoropowski, G. ; Scheuer, P.J. *J. Org. Chem.* **1998**, *63*, 3281-3286.
56 Wright, A.E. ; Chiles, S.A. ; Cross, S.S. *J. Nat. Prod.* **1991**, *54*, 1694-1686.
57 Walker, R.P. ; Faulkner, D.J. *J. Am. Chem. Soc.* **1981**, *103*, 6772-6773.
58 Keifer, P.A. ; Schwartz, R.E. ; Koker, M.E.S. ; Hughes, R.G. ; Rittschof, D. ; Rinehart, K.L. *J. Org. Chem.* **1991**, *56*, 2965-2975.
59 Eder, C. ; Proksch, P. ; Wray, V. ; van Soest, R.W.M. ; Ferdinandus, E. ; Pattissina, L.A. ; Sudarsono *J. Nat. Prod.* **1999**, *62*, 1295-1297.
60 Baran, P.S. ; Zografos, A.L. ; O'Malley, D.P. *J. Am. Chem. Soc.* **2004**, *126*, 3726-3727.
61 Nelsen, S.F., Calabrese, J.C. *J. Am. Chem. Soc.* **1973**, *95*, 8385-8388.
62 Prinzbach, H. ; Vogel, P. Auge, W. *Chimia* **1967**, *21*, 469.
63 Birman, V.B. ; Jiang, X.-T. *Org. Lett.* **2004**, *6*, 2369-2371.
64 Uemoto, H. ; Tsuda, M. ; Kobayashi, J. *J. Nat. Prod.* **1999**, *62*, 1581-1583.
65 Assmann, M. ; Zea, S. ; Köck, M. *J. Nat. Prod.* **2001**, *64*, 1593-1595.
66 Tsuda, M. ; Uemoto, H. ; Kobayashi, J. *Tetrahedron Lett.* **1999**, *40*, 5709-5712.
67 Anderson, G.T. ; Chase, C.E.. Koh, Y.-H. ; Stien, D. ; Weinreb, S.M. *J. Org. Chem.* **1998**, *63*, 7594-7595.
68 Stien, D. ; Anderson, G.T. ; Chase, C.E. ; Koh, Y.-H. ; Weinreb, S.M. *J. Am. Chem. Soc.* **1999**, *121*, 9574-9579.
69 Weinreb, S.M. ; Demko, D.M. ; Lessen, T. *Tetrahedron Lett.* **1986**, *27*, 2099-2102.
70 Weinreb, S.M. ; Chase, C.E. ; Wipf, P. ; Venkatraman, S. *Org. Synth.* **1997**, *75*, 161-164.
71 Grehn, L. ; Ragnarsson, U. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 296-301.
72 Martina, S. ; Enkelmann, V. ; Wegner, G. ; Schlüter, A.-D. *Synthesis* **1991**, 613-615.
73 Rawal, V.H. ; Jones, R.J. ; Cava, M.P. *J. Org. Chem.* **1987**, *52*, 19-28.
74 Feldman, K.S. ; Saunders, J.C. *J. Am. Chem. Soc.* **2002**, *124*, 9060-9061.
75 Feldman, K.S. ; Saunders, J.C. ; Laci Wrobleski, M. *J. Org. Chem.* **2002**, *67*, 7096-7109.
76 Oichiai, M. ; Kunishima, M. ; Nagao, Y. ; Fuji, K. ; Shiro, M. ; Fujita, E. *J. Am. Chem. Soc.* **1986**, *108*, 8281-8283.
77 Stang, P.J. ; Zhdankin, V.V. *J. Am. Chem. Soc.* **1991**, *113*, 4571-4576.
78 Feldman, K.S. *Arkivoc* **2003**, 179-190.
79 Fujisawa, T. ; Nagai, M. ; Koike, Y. ; Shimizu, M. *J. Org. Chem.* **1999**, *59*, 5865-5867.
80 Warner, B.P. ; Buchwald, S.L. *J. Org. Chem.* **1994**, *59*, 5822-5823.
81 Yoakim, C. ; Ogilvie, W.W. ; Cameron, D.R. ; Chabot, C. ; Guse, I.. Haché, B. ; Naud, J. ; O'Meara, J.A. ; Déziel, R. *J. Med. Chem.* **1998**, *41*, 2882-2891.
82 Takano, S. ; Kamikubo, T. ; Sugihara, T. ; Ogasawara, K. *Tetrahedron : Asymm.* **1992**, *3*, 853-856.

83 Furrow, M.E. ; Schauss, S.E. ; Jacobsen, E.N. *J. Org. Chem.* **1998**, *63*, 6776-6777.
84 Baron, E. ; O'Brien, P. ; Towers, T.D. *Tetrahedron Lett.* **2002**, *43*, 723-726.
85 Knight, J.G. ; Muldowney, M.P. *Synlett* **1995**, 945-951.
86 Haudrechy, A. ; Sinaÿ, P. *J. Org. Chem.* **1992**, *57*, 4142-4151.
87 Bernet, B. ; Vasella, A. *Helv. Chim. Acta.* **1979**, *62*, 1990-2016.
88 Gibbs, C.F. ; Hough, L. ; Richardson, A.C. *Carbohydrate Res.* **1965**, *1*, 290-296.
89 Inouye, Y. ; Onodera, K. ; Kitaoka, S. ;Hirano, S. *J. Am. Chem. Soc.* **1956**, *78*, 4722-4724.
90 Ali, Y. ; Richardson, A.C. ; Gibbs, C.F. ; Hough, L. *Carbohydrate Res.* **1968**, *7*, 255-271.
91 Charon, D.; Mondage, M.; Pons, J-F.; Le Bray, K.; Chaby, R. *Biorg. Med. Chem.* **1998**, *6*, 755.
92 Huang, J. ; Widlanski, T.S. *Tetrahedron Lett.*, **1992**, *33*, 2657-2660.
93 Parker, L.L.; Gowans, N.D.; Jones, S.W.; Robins, D.J. *Tetrahedron* **2003**, *59*, 10165-10171.
94 Carpino, L.A. ; Cohen, B.J. ; Stephens, K.E. ; Sadat-Aalaee, S.Y. ; Tien, T.H. ; Langridge, D.C. *J. Org. Chem.* **1986**, *51*, 3732-3734.
95 Hanessian, S. ; Lavallee, P. *Carbohydrate Res.* **1973**, *28*, 303-311.
96 Anisuzzaman, A.K.M. ; Whistler, R.L. *Carbohydrate Res.* **1978**, *61*, 511-518.
97 Garegg, P.J. ; Samuelsson, B. *J. Chem. Soc., Chem. Commun.* **1979**, 978-980.
98 Tebbe, F.N. ; Parshall, G.W. ; Reddy, G.S. *J. Am. Chem. Soc.* **1978**, *100*, 3611-3613.
99 Takai, K. ; Kakiuchi, T. ; Kataoka, Y. ; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 2668-2670.
100 Blakemore, P.R. ; Cole, W.J., Kocienski, P.J. ; Morley, A. *Synlett* **1998**, 26-28.
101 Baudin, J.B.; Hareau, G.; Julia, S.A.; Ruel, O. *Tetrahedron Lett.* **1991**, *32*, 1175-1178.
102 Blakemore, P.R. ; Kocienski, P.J. ; Morley, A. ; Muir, K. *J. Chem. Soc., Perkin Trans. 1* **1999**, 955-968.
103 Nelson, T.D.; Crouch, R.D. *Synthesis* **1996**, 1031-1069.
104 Fürstner, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3012-3043.
105 Schwab, P. ; Grubbs, R.H. ; Ziller, J.W. *J. Am. Chem. Soc.* **1996**, *118*, 100-110.
106 Scholl, M. ; Trnka, T.M. ; Morgan, J.P. ; Grubbs, R.H. *Tetrahedron Lett.* **1999**, *40*, 2247-2250.
107 Scholl, M. ; Ding, S. ; Lee, C.W. ; Grubbs, R.H. *Org. Lett.* **1999**, *1*, 953-956.
108 Michrowska, A. ; Bujok, R. ; Harutyunyan, S. ; Sashuk, V.; Dolgonos, G.; Grela, K. *J. Am. Chem. Soc.* **2004**, *126*, 9318-9325.
109 Garber, S.B. ; Kingsbury, J.S. ; Gray, B.L. ; Hoveyda, A.H. *J. Am. Chem. Soc.* **2000**, *122*, 8168-8179.
110 Ward, D.E. ; Gai, Y. ; Kaller, B.F. *J. Org. Chem.* **1996**, *61*, 5498-5505.
111 Campbell, J.A. ; Hart, D.J. *J. Org. Chem.* **1993**, *58*, 2900-2903.
112 Hartung, J. ; Hünig, S. ; Kneuer, R. ; Schwarz, M. ; Wenner, H. *Synthesis* **1997**, 1433-1438.
113 Durette, P.L. ; Baker, F. ; Barker, P.L. ; Boger, J. ; Bondy, S.S. ; Hammond, M.L. ; Lanza, T.J. ; Pessolano, A.A. ; Caldwell, C.G. *Tetrahedron Lett.* **1990**, *31*, 1237-1240.
114 Hale, K.J. ; Lazarides, L. ; Cai, J. *Org. Lett.* **2001**, *3*, 2927-2930.
115 Hale, K.J. ; Lazarides, L. *Org. Lett* **2002**, *4*, 1903-1906.
116 Smith, R.M. ; Weiner, D.P. ; Chatuverdi, N.C. ; Thimblin, M.D. ; Raymond, S.J. ; Hansen, D.E. *Bioorg. Chem.* **1995**, *23*, 397-414.
117 Roberts, S.M. ; Newton, R.F. In *Prostaglandins and Thromboxanes;* Roberts, S.M., Newton, R.F., Eds.; Butterworths, 1982; Chapter 6, p86.
118 Heathcock, C.H., Smith, S.C. *J. Org. Chem.* **1992**, *57*, 6379-6380.
119 Smith, S.C., Heathcock, C.H. *J. Org. Chem.* **1994**, *59*, 6828-6839.
120 Smith III, A.B. ; Hale, K.J. ; McCauley Jr., J.P. *Tetrahedron Lett.* **1989**, *30*, 5579-5582.
121 Parsons, A.F. ; Pettifer, R.M. *Tetrahedron Lett.* **1996**, *37*, 1667-1670.
122 Stewart, I.C. ; Bergman, R.G. ; Toste, F.D. *J. Am. Chem. Soc.* **2003**, *125*, 8696-8697.
123 Meijer, L.; Thunnissen, A.M.; White, A.W.; Garnier, M.; Nikolic, M.; Tsai, L.H.; Walter, J.; Cleverley, K.E.; Salinas, P.C.; Wu, Y.Z. ; Biernat, J.; Mandelkow, E.-M.; Kim, S.-H.; Pettit, G.R. *Chem. Biol* **2000**, *7*, 51-63.
124 Embi, N.; Rylatt, D.B.; Cohen, P. *Eur. J. Biochem.* **1980**, *107*, 519-527.
125 Ryves, W.J.; Harwood, A.J. *Biochem. Biophys. Res. Commun.* **2001**, *280*, 720-725.
126 Finkelman-Eldar, H. *Trends Mol. Med.* **2002**, *8*, 126-132.

Appendix 1

X-Ray Diffraction Data for Compounds (-)-**150** and (-)-**310**

Table 6. Crystal data and structure refinement for (-)-**150**.

Identification code	str0121	
Chemical formula	$C_{16}H_{28}N_2O_6SSi$	
Formula weight	404.55	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	orthorhombic, $P2_12_12_1$	
Unit cell parameters	a = 6.334(2) Å	α = 90°
	b = 10.812(4) Å	β = 90°
	c = 31.745(12) Å	γ = 90°
Cell volume	2173.9(14) $Å^3$	
Z	4	
Calculated density	1.236 g/cm^3	
Absorption coefficient μ	0.235 mm^{-1}	
F(000)	864	
Crystal colour and size	colourless, 0.42 × 0.22 × 0.08 mm^3	
Data collection method	Bruker SMART APEX diffractometer	
	ω rotation with narrow frames	
θ range for data collection	1.99 to 28.49°	
Index ranges	h −8 to 8, k −14 to 14, l −41 to 41	
Completeness to θ = 26.00°	99.6 %	
Reflections collected	17159	
Independent reflections	5096 (R_{int} = 0.0997)	
Reflections with $F^2>2\sigma$	4174	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.9077 and 0.9814	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0472, 11.5798	
Data / restraints / parameters	5096 / 0 / 244	
Final R indices [$F^2>2\sigma$]	R1 = 0.1119, wR2 = 0.2249	
R indices (all data)	R1 = 0.1326, wR2 = 0.2344	
Goodness-of-fit on F^2	1.117	
Absolute structure parameter	0.0(2)	
Largest and mean shift/su	0.004 and 0.001	
Largest diff. peak and hole	1.007 and −0.646 e $Å^{-3}$	

Table 7. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for (-)-**150**. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
S(1)	0.7947(3)	0.70405(13)	0.06118(5)	0.0192(3)
Si(2)	0.5054(4)	1.01360(16)	0.13409(7)	0.0328(5)
O(1)	0.9225(8)	0.7780(4)	0.03368(16)	0.0300(12)
O(2)	0.8991(8)	0.6344(4)	0.09357(15)	0.0248(11)
O(3)	0.0409(7)	0.3883(4)	0.03380(15)	0.0230(10)
O(4)	–0.0526(8)	0.3146(4)	0.09666(16)	0.0308(12)
O(5)	0.1910(9)	0.4154(4)	0.15746(14)	0.0302(11)
O(6)	0.3825(8)	0.5796(4)	0.13554(15)	0.0276(11)
N(1)	0.6746(9)	0.6072(5)	0.03018(17)	0.0191(11)
N(2)	0.2407(8)	0.4487(4)	0.08846(17)	0.0165(11)
C(1)	0.651(2)	1.1299(8)	0.1671(3)	0.069(4)
C(2)	0.3627(18)	1.0929(9)	0.0911(3)	0.069(3)
C(3)	0.3121(17)	0.9234(8)	0.1663(3)	0.051(2)
C(4)	0.7106(13)	0.9050(5)	0.1111(2)	0.0291(16)
C(5)	0.6034(10)	0.8030(6)	0.0845(2)	0.0223(13)
C(6)	0.5580(9)	0.4996(5)	0.04562(19)	0.0154(12)
C(7)	0.5548(10)	0.4053(5)	0.0104(2)	0.0196(13)
C(8)	0.3682(10)	0.3924(5)	–0.0066(2)	0.0188(13)
C(9)	0.2045(12)	0.4674(5)	0.0155(2)	0.0232(14)
C(10)	0.3216(10)	0.5227(5)	0.05371(17)	0.0163(12)
C(11)	0.0683(11)	0.3773(5)	0.0755(2)	0.0216(14)
C(12)	0.2762(10)	0.4877(5)	0.1289(2)	0.0240(14)
C(13)	0.1941(16)	0.4504(7)	0.2023(2)	0.0378(19)
C(14)	0.073(2)	0.3443(9)	0.2227(3)	0.063(3)
C(15)	0.0667(19)	0.5693(9)	0.2070(3)	0.061(3)
C(16)	0.4173(15)	0.4625(9)	0.2187(3)	0.049(2)

Table 8. Bond lengths [Å] and angles [°] for (-)-**150**.

S(1)–O(1)	1.434(5)	S(1)–O(2)	1.436(5)
S(1)–N(1)	1.626(5)	S(1)–C(5)	1.778(6)
Si(2)–C(2)	1.848(10)	Si(2)–C(3)	1.870(9)
Si(2)–C(1)	1.880(9)	Si(2)–C(4)	1.898(7)
O(3)–C(11)	1.340(8)	O(3)–C(9)	1.464(8)
O(4)–C(11)	1.223(8)	O(5)–C(12)	1.314(8)
O(5)–C(13)	1.474(9)	O(6)–C(12)	1.218(8)
N(1)–C(6)	1.463(7)	N(2)–C(12)	1.369(8)
N(2)–C(11)	1.399(8)	N(2)–C(10)	1.456(7)
C(4)–C(5)	1.546(9)	C(6)–C(7)	1.514(8)
C(6)–C(10)	1.539(8)	C(7)–C(8)	1.306(9)
C(8)–C(9)	1.491(9)	C(9)–C(10)	1.542(8)
C(13)–C(16)	1.513(13)	C(13)–C(15)	1.524(12)
C(13)–C(14)	1.526(11)		

O(1)–S(1)–O(2)	117.9(3)	O(1)–S(1)–N(1)	104.7(3)
O(2)–S(1)–N(1)	108.1(3)	O(1)–S(1)–C(5)	107.6(3)
O(2)–S(1)–C(5)	109.4(3)	N(1)–S(1)–C(5)	108.7(3)
C(2)–Si(2)–C(3)	109.0(5)	C(2)–Si(2)–C(1)	110.0(5)
C(3)–Si(2)–C(1)	111.5(4)	C(2)–Si(2)–C(4)	109.7(4)
C(3)–Si(2)–C(4)	109.6(4)	C(1)–Si(2)–C(4)	106.9(5)
C(11)–O(3)–C(9)	110.6(5)	C(12)–O(5)–C(13)	120.6(5)
C(6)–N(1)–S(1)	123.1(4)	C(12)–N(2)–C(11)	125.0(5)
C(12)–N(2)–C(10)	118.9(5)	C(11)–N(2)–C(10)	110.8(5)
C(5)–C(4)–Si(2)	110.5(5)	C(4)–C(5)–S(1)	110.9(5)
N(1)–C(6)–C(7)	107.1(5)	N(1)–C(6)–C(10)	114.7(5)
C(7)–C(6)–C(10)	102.7(5)	C(8)–C(7)–C(6)	112.9(5)
C(7)–C(8)–C(9)	112.1(6)	O(3)–C(9)–C(8)	111.2(5)
O(3)–C(9)–C(10)	104.8(5)	C(8)–C(9)–C(10)	104.3(6)
N(2)–C(10)–C(6)	112.3(5)	N(2)–C(10)–C(9)	102.3(5)
C(6)–C(10)–C(9)	105.9(5)	O(4)–C(11)–O(3)	120.7(6)
O(4)–C(11)–N(2)	129.2(6)	O(3)–C(11)–N(2)	110.0(5)
O(6)–C(12)–O(5)	126.3(7)	O(6)–C(12)–N(2)	120.3(6)
O(5)–C(12)–N(2)	113.3(6)	O(5)–C(13)–C(16)	111.6(7)
O(5)–C(13)–C(15)	107.7(7)	C(16)–C(13)–C(15)	112.9(8)
O(5)–C(13)–C(14)	102.0(6)	C(16)–C(13)–C(14)	113.0(8)
C(15)–C(13)–C(14)	109.0(8)		

Table 9. Anisotropic displacement parameters ($Å^2$) for (-)-**150**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ...+ 2hka^*b^*U^{12}]$

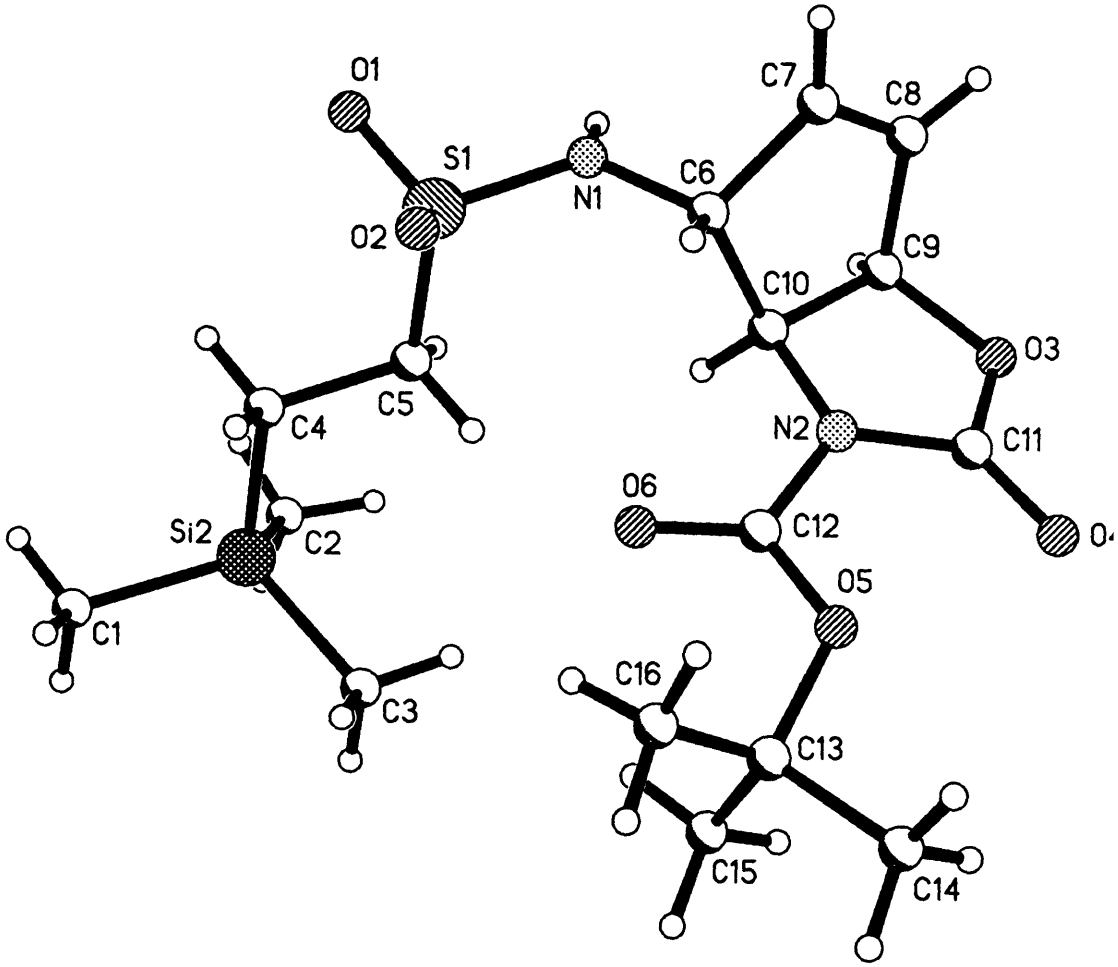
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	0.0209(7)	0.0087(6)	0.0279(8)	0.0011(6)	0.0017(7)	–0.0007(6)
Si(2)	0.0522(13)	0.0113(8)	0.0348(11)	–0.0012(8)	0.0073(10)	0.0060(9)
O(1)	0.028(3)	0.016(2)	0.047(3)	0.001(2)	0.012(2)	–0.013(2)
O(2)	0.025(3)	0.013(2)	0.036(3)	–0.0023(19)	–0.009(2)	0.0055(19)
O(3)	0.017(2)	0.015(2)	0.037(3)	–0.0040(19)	–0.003(2)	0.0000(18)
O(4)	0.029(3)	0.012(2)	0.051(3)	0.006(2)	0.002(2)	–0.004(2)
O(5)	0.044(3)	0.018(2)	0.028(3)	0.0023(19)	0.002(2)	–0.009(2)
O(6)	0.037(3)	0.019(2)	0.027(3)	–0.003(2)	0.000(2)	–0.011(2)
N(1)	0.025(3)	0.012(2)	0.020(3)	0.003(2)	–0.003(2)	0.000(2)
N(2)	0.009(3)	0.013(2)	0.027(3)	0.000(2)	0.003(2)	0.0020(18)
C(1)	0.119(11)	0.025(4)	0.064(6)	–0.023(4)	0.030(7)	–0.038(6)
C(2)	0.082(8)	0.050(6)	0.074(7)	0.008(5)	0.005(6)	0.044(6)
C(3)	0.062(6)	0.039(5)	0.052(5)	–0.001(4)	0.015(5)	0.001(5)
C(4)	0.033(4)	0.008(3)	0.047(4)	–0.003(3)	0.003(4)	–0.005(3)
C(5)	0.019(3)	0.012(3)	0.036(4)	–0.002(3)	0.001(3)	0.006(3)
C(6)	0.011(3)	0.006(2)	0.030(3)	0.004(2)	0.001(2)	–0.002(2)
C(7)	0.021(3)	0.014(3)	0.024(3)	–0.004(2)	0.000(3)	0.008(2)
C(8)	0.027(3)	0.008(3)	0.022(3)	–0.003(2)	0.001(3)	0.004(2)
C(9)	0.033(4)	0.011(3)	0.025(3)	0.003(2)	–0.002(3)	0.000(3)
C(10)	0.027(3)	0.007(2)	0.015(3)	0.001(2)	0.002(3)	–0.003(2)
C(11)	0.024(3)	0.003(2)	0.038(4)	–0.005(2)	0.011(3)	0.000(2)
C(12)	0.018(3)	0.013(3)	0.041(4)	0.004(3)	0.008(3)	0.002(3)
C(13)	0.056(5)	0.024(3)	0.033(4)	0.005(3)	0.014(4)	0.002(4)
C(14)	0.106(9)	0.048(5)	0.035(5)	0.010(4)	0.024(6)	–0.017(6)
C(15)	0.091(9)	0.052(5)	0.039(5)	–0.013(4)	0.019(5)	0.016(6)
C(16)	0.054(6)	0.050(5)	0.043(5)	–0.005(4)	–0.010(4)	0.002(4)

Table 10. Hydrogen coordinates and isotropic displacement parameters ($Å^2$) for (-)-**150**.

	x	y	z	U
H(1N)	0.632(17)	0.639(10)	0.005(3)	0.080
H(1A)	0.5507	1.1887	0.1792	0.104
H(1B)	0.7528	1.1746	0.1494	0.104
H(1C)	0.7269	1.0872	0.1897	0.104
H(2A)	0.2754	1.1592	0.1029	0.103
H(2B)	0.2724	1.0333	0.0764	0.103
H(2C)	0.4647	1.1281	0.0712	0.103
H(3A)	0.3864	0.8816	0.1893	0.077
H(3B)	0.2426	0.8616	0.1484	0.077
H(3C)	0.2058	0.9796	0.1780	0.077
H(4A)	0.8097	0.9524	0.0932	0.035
H(4B)	0.7926	0.8664	0.1342	0.035
H(5A)	0.5169	0.8417	0.0621	0.027
H(5B)	0.5084	0.7537	0.1027	0.027
H(6)	0.6273	0.4645	0.0713	0.018
H(7)	0.6757	0.3602	0.0015	0.024
H(8)	0.3400	0.3412	–0.0303	0.023
H(9)	0.1436	0.5329	–0.0031	0.028
H(10)	0.2898	0.6126	0.0574	0.020
H(14A)	–0.0680	0.3382	0.2099	0.094
H(14B)	0.0584	0.3597	0.2530	0.094
H(14C)	0.1492	0.2666	0.2182	0.094
H(15A)	0.1407	0.6371	0.1928	0.091
H(15B)	0.0505	0.5890	0.2370	0.091
H(15C)	–0.0729	0.5581	0.1942	0.091
H(16A)	0.5002	0.3906	0.2099	0.073
H(16B)	0.4148	0.4667	0.2496	0.073
H(16C)	0.4815	0.5380	0.2074	0.073

Table 11. Torsion angles [°] for (-)-**150**.

O(1)–S(1)–N(1)–C(6)	168.3(5)	O(2)–S(1)–N(1)–C(6)	41.8(6)
C(5)–S(1)–N(1)–C(6)	−76.9(5)	C(2)–Si(2)–C(4)–C(5)	−62.6(6)
C(3)–Si(2)–C(4)–C(5)	57.1(6)	C(1)–Si(2)–C(4)–C(5)	178.2(5)
Si(2)–C(4)–C(5)–S(1)	177.8(3)	O(1)–S(1)–C(5)–C(4)	−61.8(5)
O(2)–S(1)–C(5)–C(4)	67.5(5)	N(1)–S(1)–C(5)–C(4)	−174.7(4)
S(1)–N(1)–C(6)–C(7)	−155.2(4)	S(1)–N(1)–C(6)–C(10)	91.6(6)
N(1)–C(6)–C(7)–C(8)	−109.2(6)	C(10)–C(6)–C(7)–C(8)	12.0(7)
C(6)–C(7)–C(8)–C(9)	−4.3(8)	C(11)–O(3)–C(9)–C(8)	103.2(6)
C(11)–O(3)–C(9)–C(10)	−8.8(6)	C(7)–C(8)–C(9)–O(3)	−117.8(6)
C(7)–C(8)–C(9)–C(10)	−5.4(7)	C(12)–N(2)–C(10)–C(6)	80.3(6)
C(11)–N(2)–C(10)–C(6)	−124.2(5)	C(12)–N(2)–C(10)–C(9)	−166.6(5)
C(11)–N(2)–C(10)–C(9)	−11.1(6)	N(1)–C(6)–C(10)–N(2)	−147.7(5)
C(7)–C(6)–C(10)–N(2)	96.5(5)	N(1)–C(6)–C(10)–C(9)	101.4(5)
C(7)–C(6)–C(10)–C(9)	−14.4(6)	O(3)–C(9)–C(10)–N(2)	11.6(6)
C(8)–C(9)–C(10)–N(2)	−105.3(5)	O(3)–C(9)–C(10)–C(6)	129.4(5)
C(8)–C(9)–C(10)–C(6)	12.5(6)	C(9)–O(3)–C(11)–O(4)	−179.9(5)
C(9)–O(3)–C(11)–N(2)	2.1(7)	C(12)–N(2)–C(11)–O(4)	−17.9(10)
C(10)–N(2)–C(11)–O(4)	−171.5(6)	C(12)–N(2)–C(11)–O(3)	159.9(5)
C(10)–N(2)–C(11)–O(3)	6.2(7)	C(13)–O(5)–C(12)–O(6)	8.5(11)
C(13)–O(5)–C(12)–N(2)	−173.5(6)	C(11)–N(2)–C(12)–O(6)	−155.3(6)
C(10)–N(2)–C(12)–O(6)	−3.6(9)	C(11)–N(2)–C(12)–O(5)	26.5(8)
C(10)–N(2)–C(12)–O(5)	178.3(5)	C(12)–O(5)–C(13)–C(16)	−61.3(9)
C(12)–O(5)–C(13)–C(15)	63.0(10)	C(12)–O(5)–C(13)–C(14)	177.8(7)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O2
N1
C6
C7
C8
C9
C10
O3
C5
C4
N2
C11
O6
C12
O4
Si2
C2
O5
C1
C16
C3
C13
C15
C14

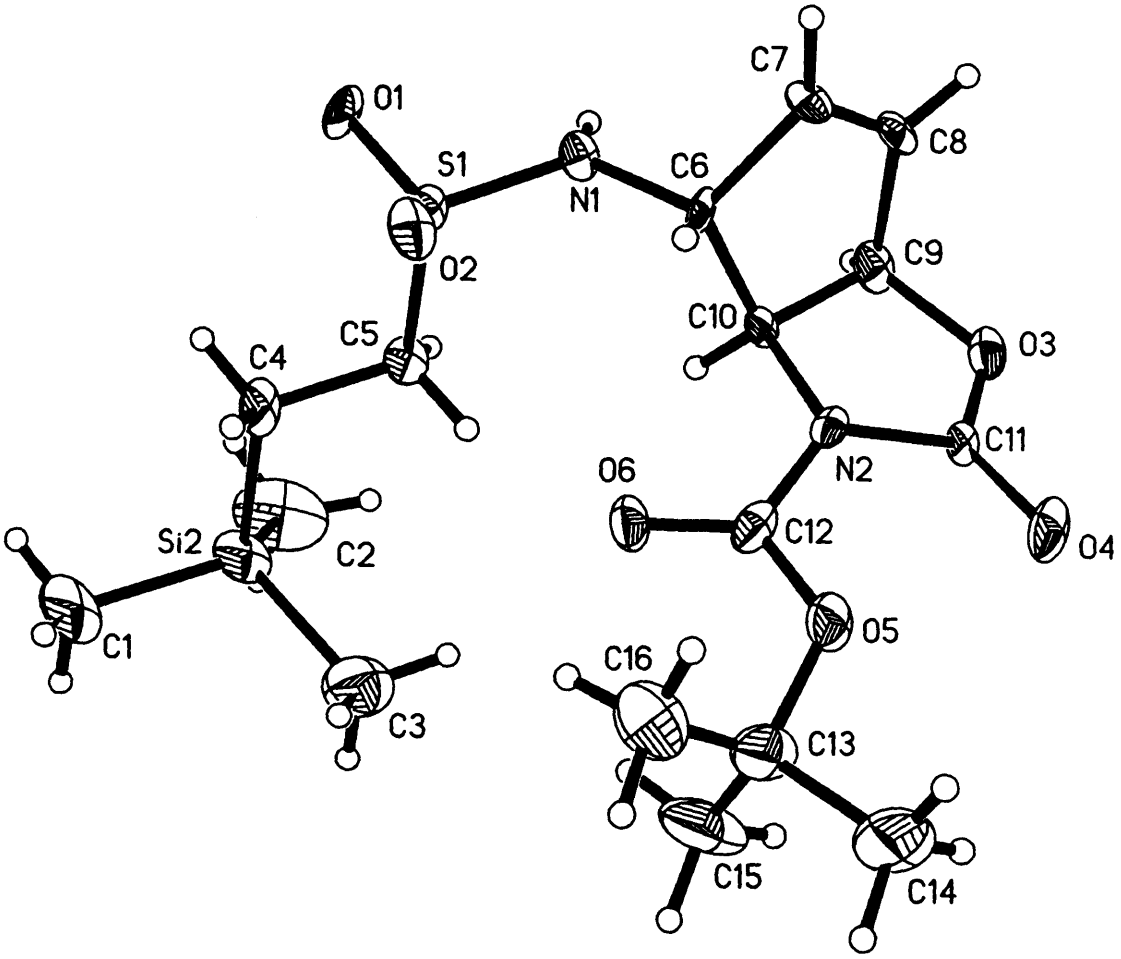

C7
O1
C8
S1
N1
C6
O2
C9
C10
C5
O3
C4
N2
C11
O6
C12
O4
Si2
C2
C1
O5
C16
C3
C13
C15
C14

Table 12. Crystal data and structure refinement for (-)-**310**.

Identification code	str0187	
Chemical formula	$C_{20}H_{29}N_3O_5SSi$	
Formula weight	451.61	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	monoclinic, $P2_1$	
Unit cell parameters	a = 12.4381(10) Å	α = 90°
	b = 6.2678(5) Å	β = 97.990(2)°
	c = 15.0769(12) Å	γ = 90°
Cell volume	1163.98(16) Å^3	
Z	2	
Calculated density	1.289 g/cm^3	
Absorption coefficient μ	0.225 mm^{-1}	
F(000)	480	
Crystal colour and size	colourless, 0.50 × 0.20 × 0.16 mm^3	
Data collection method	Bruker SMART APEX diffractometer	
	ω rotation with narrow frames	
θ range for data collection	1.65 to 28.25°	
Index ranges	h −15 to 15, k −8 to 8, l −20 to 14	
Completeness to θ = 26.00°	98.3 %	
Reflections collected	6227	
Independent reflections	4826 (R_{int} = 0.0177)	
Reflections with $F^2>2\sigma$	4731	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.8957 and 0.9648	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0574, 0.1856	
Data / restraints / parameters	4826 / 1 / 271	
Final R indices [$F^2>2\sigma$]	R1 = 0.0348, wR2 = 0.0921	
R indices (all data)	R1 = 0.0355, wR2 = 0.0928	
Goodness-of-fit on F^2	1.023	
Absolute structure parameter	0.04(6)	
Largest and mean shift/su	0.000 and 0.000	
Largest diff. peak and hole	0.349 and −0.255 e Å^{-3}	

Table 13. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for (-)-**310**. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
S(1)	0.42020(4)	1.26940(7)	0.87967(3)	0.02652(11)
Si(2)	0.57368(4)	0.79909(8)	0.71157(3)	0.02460(12)
O(1)	0.34676(13)	1.4332(2)	0.84217(11)	0.0403(4)
O(2)	0.52451(11)	1.3284(3)	0.92819(10)	0.0417(4)
O(3)	0.11973(11)	0.5624(2)	0.94241(10)	0.0345(3)
O(4)	–0.00575(13)	0.5503(3)	0.81970(10)	0.0440(4)
O(5)	0.19758(10)	0.8834(3)	0.70685(9)	0.0380(4)
N(1)	0.35998(11)	1.1361(3)	0.95025(10)	0.0239(3)
N(2)	0.12990(11)	0.8076(3)	0.83683(9)	0.0260(3)
N(3)	0.02074(12)	0.9659(3)	0.71566(11)	0.0293(3)
C(1)	0.63089(17)	1.0121(4)	0.64490(15)	0.0384(5)
C(2)	0.67671(15)	0.5921(4)	0.75149(14)	0.0329(4)
C(3)	0.45622(18)	0.6689(4)	0.64294(17)	0.0460(6)
C(4)	0.52819(14)	0.9275(3)	0.81330(12)	0.0288(4)
C(5)	0.44472(14)	1.1026(3)	0.78890(12)	0.0259(4)
C(6)	0.24569(13)	1.0691(3)	0.92851(11)	0.0218(3)
C(7)	0.19284(15)	1.0646(3)	1.01306(13)	0.0293(4)
C(8)	0.17492(16)	0.8681(4)	1.03920(13)	0.0331(4)
C(9)	0.20903(15)	0.7030(3)	0.97685(13)	0.0293(4)
C(10)	0.23321(13)	0.8364(3)	0.89538(11)	0.0224(3)
C(11)	0.07262(16)	0.6328(3)	0.86082(13)	0.0319(4)
C(12)	0.11900(14)	0.8864(3)	0.74684(12)	0.0267(4)
C(13)	–0.06321(15)	1.0169(4)	0.77103(14)	0.0366(5)
C(14)	0.00004(15)	1.0331(4)	0.62177(14)	0.0350(5)
C(15)	–0.08872(14)	0.9057(4)	0.56602(13)	0.0297(4)
C(16)	–0.11977(15)	0.7049(4)	0.59141(14)	0.0325(4)
C(17)	–0.20111(16)	0.5931(4)	0.53635(15)	0.0403(5)
C(18)	–0.24961(16)	0.6829(5)	0.45656(16)	0.0452(6)
C(19)	–0.21650(16)	0.8798(5)	0.43057(15)	0.0449(6)
C(20)	–0.13749(15)	0.9935(4)	0.48497(14)	0.0355(5)

Table 14. Bond lengths [Å] and angles [°] for (-)-**310**.

S(1)–O(1)	1.4366(16)	S(1)–O(2)	1.4461(1
S(1)–N(1)	1.6164(16)	S(1)–C(5)	1.7819(1
Si(2)–C(3)	1.857(2)	Si(2)–C(2)	1.864(2)
Si(2)–C(1)	1.870(2)	Si(2)–C(4)	1.8872(1
O(3)–C(11)	1.360(2)	O(3)–C(9)	1.456(2)
O(4)–C(11)	1.197(2)	O(5)–C(12)	1.218(2)
N(1)–C(6)	1.475(2)	N(2)–C(11)	1.382(2)
N(2)–C(12)	1.432(2)	N(2)–C(10)	1.465(2)
N(3)–C(12)	1.343(2)	N(3)–C(13)	1.460(3)
N(3)–C(14)	1.465(2)	C(4)–C(5)	1.520(3)
C(6)–C(7)	1.514(2)	C(6)–C(10)	1.542(3)
C(7)–C(8)	1.322(3)	C(8)–C(9)	1.498(3)
C(9)–C(10)	1.549(3)	C(14)–C(15)	1.518(3)
C(15)–C(16)	1.385(3)	C(15)–C(20)	1.399(3)
C(16)–C(17)	1.404(3)	C(17)–C(18)	1.388(3)
C(18)–C(19)	1.375(4)	C(19)–C(20)	1.387(3)
O(1)–S(1)–O(2)	119.54(10)	O(1)–S(1)–N(1)	107.51(8)
O(2)–S(1)–N(1)	105.32(9)	O(1)–S(1)–C(5)	106.52(9)
O(2)–S(1)–C(5)	107.54(9)	N(1)–S(1)–C(5)	110.29(9)
C(3)–Si(2)–C(2)	109.05(11)	C(3)–Si(2)–C(1)	110.04(11)
C(2)–Si(2)–C(1)	112.00(9)	C(3)–Si(2)–C(4)	109.80(10)
C(2)–Si(2)–C(4)	107.75(9)	C(1)–Si(2)–C(4)	108.16(10)
C(11)–O(3)–C(9)	109.73(15)	C(6)–N(1)–S(1)	121.43(12)
C(11)–N(2)–C(12)	122.46(15)	C(11)–N(2)–C(10)	112.37(15)
C(12)–N(2)–C(10)	119.19(14)	C(12)–N(3)–C(13)	124.71(16)
C(12)–N(3)–C(14)	118.30(16)	C(13)–N(3)–C(14)	116.48(17)
C(5)–C(4)–Si(2)	112.52(13)	C(4)–C(5)–S(1)	114.94(13)
N(1)–C(6)–C(7)	109.64(14)	N(1)–C(6)–C(10)	113.07(14)
C(7)–C(6)–C(10)	102.67(15)	C(8)–C(7)–C(6)	112.29(18)
C(7)–C(8)–C(9)	112.48(17)	O(3)–C(9)–C(8)	111.91(15)
O(3)–C(9)–C(10)	105.45(14)	C(8)–C(9)–C(10)	103.17(16)
N(2)–C(10)–C(6)	110.60(14)	N(2)–C(10)–C(9)	99.24(13)
C(6)–C(10)–C(9)	105.98(14)	O(4)–C(11)–O(3)	123.05(19)
O(4)–C(11)–N(2)	128.24(19)	O(3)–C(11)–N(2)	108.71(16)
O(5)–C(12)–N(3)	125.90(17)	O(5)–C(12)–N(2)	119.13(16)
N(3)–C(12)–N(2)	114.92(16)	N(3)–C(14)–C(15)	113.60(17)
C(16)–C(15)–C(20)	119.7(2)	C(16)–C(15)–C(14)	122.27(18)
C(20)–C(15)–C(14)	118.0(2)	C(15)–C(16)–C(17)	119.7(2)
C(18)–C(17)–C(16)	120.1(2)	C(19)–C(18)–C(17)	120.0(2)
C(18)–C(19)–C(20)	120.6(2)	C(19)–C(20)–C(15)	120.0(2)

Table 15. Anisotropic displacement parameters ($Å^2$) for (-)-**310**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ...+ 2hka^*b^*U^{12}]$

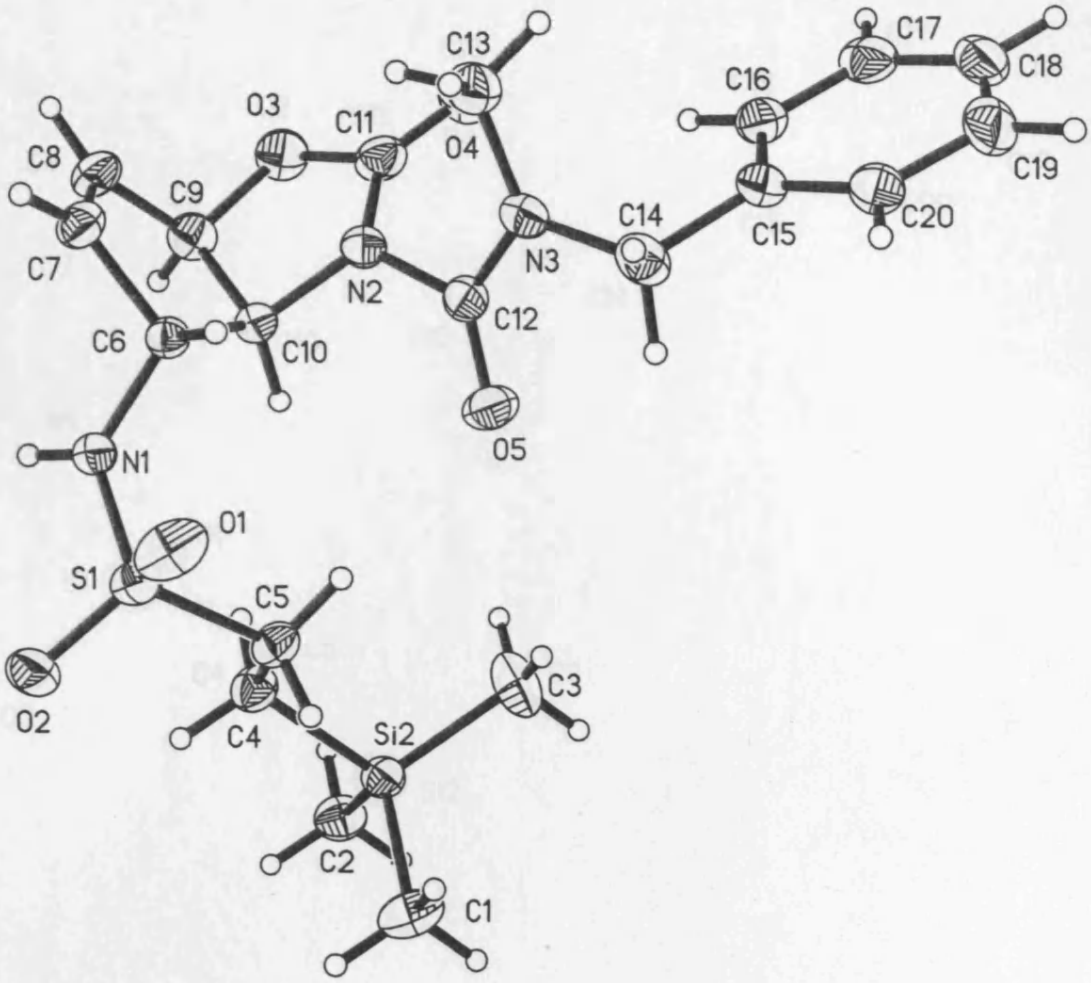
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	0.0309(2)	0.0200(2)	0.0309(2)	−0.00339(17)	0.01194(16)	
	−0.00312(17)					
Si(2)	0.0235(2)	0.0242(3)	0.0266(2)	−0.0028(2)	0.00506(17)	
	0.00070(19)					
O(1)	0.0558(9)	0.0238(7)	0.0460(8)	0.0074(7)	0.0233(7)	0.0079(7)
O(2)	0.0361(7)	0.0449(10)	0.0470(8)	−0.0182(7)	0.0150(6)	−0.0186(7)
O(3)	0.0418(7)	0.0269(7)	0.0355(7)	0.0053(6)	0.0080(6)	−0.0090(6)
O(4)	0.0474(8)	0.0438(9)	0.0411(8)	0.0009(8)	0.0074(7)	−0.0229(8)
O(5)	0.0283(6)	0.0566(10)	0.0307(7)	0.0094(7)	0.0096(6)	0.0029(7)
N(1)	0.0223(6)	0.0269(8)	0.0228(7)	0.0008(6)	0.0040(5)	−0.0016(6)
N(2)	0.0256(6)	0.0287(8)	0.0241(7)	0.0010(6)	0.0053(5)	−0.0069(6)
N(3)	0.0228(7)	0.0351(9)	0.0300(8)	0.0004(7)	0.0035(6)	−0.0066(6)
C(1)	0.0420(11)	0.0335(11)	0.0443(12)	0.0056(9)	0.0221(9)	0.0061(9)
C(2)	0.0303(9)	0.0328(11)	0.0367(10)	0.0027(9)	0.0080(8)	0.0046(8)
C(3)	0.0414(11)	0.0414(13)	0.0501(13)	−0.0094(11)	−0.0110(10)	
−0.0015(10)						
C(4)	0.0278(8)	0.0319(10)	0.0274(9)	−0.0018(8)	0.0064(7)	0.0049(8)
C(5)	0.0294(8)	0.0245(9)	0.0253(9)	−0.0017(7)	0.0086(7)	0.0015(7)
C(6)	0.0207(7)	0.0216(9)	0.0234(8)	−0.0003(7)	0.0043(6)	0.0013(6)
C(7)	0.0301(9)	0.0311(10)	0.0282(9)	−0.0038(8)	0.0094(7)	0.0011(8)
C(8)	0.0343(9)	0.0429(12)	0.0238(8)	0.0038(8)	0.0105(8)	−0.0017(8)
C(9)	0.0313(9)	0.0255(9)	0.0313(10)	0.0061(7)	0.0050(8)	−0.0017(7)
C(10)	0.0225(7)	0.0234(9)	0.0219(8)	0.0005(6)	0.0052(6)	−0.0003(6)
C(11)	0.0360(9)	0.0309(10)	0.0310(10)	0.0005(8)	0.0123(8)	−0.0071(8)
C(12)	0.0276(8)	0.0269(9)	0.0259(8)	−0.0014(7)	0.0043(7)	−0.0048(7)
C(13)	0.0293(9)	0.0409(12)	0.0399(11)	−0.0089(9)	0.0059(8)	−0.0009(9)
C(14)	0.0279(9)	0.0401(12)	0.0355(10)	0.0087(9)	−0.0003(8)	−0.0090(8)
C(15)	0.0204(8)	0.0378(11)	0.0310(9)	−0.0022(8)	0.0043(7)	0.0012(8)
C(16)	0.0293(9)	0.0370(11)	0.0326(10)	−0.0048(8)	0.0093(8)	−0.0030(8)
C(17)	0.0348(10)	0.0443(13)	0.0447(12)	−0.0201(10)	0.0163(9)	−0.0077(9)
C(18)	0.0243(9)	0.0683(17)	0.0429(12)	−0.0284(12)	0.0042(9)	
−0.0022(10)						
C(19)	0.0276(9)	0.0691(17)	0.0364(11)	−0.0119(11)	−0.0014(8)	0.0156(11)
C(20)	0.0258(9)	0.0467(13)	0.0342(10)	−0.0014(9)	0.0046(8)	0.0082(8)

Table 16. Hydrogen coordinates and isotropic displacement parameters ($Å^2$) for (-)-**310**.

	x	y	z	U
H(1N)	0.3962	1.1028	1.0028	0.029
H(1A)	0.6550	0.9486	0.5916	0.058
H(1B)	0.6928	1.0798	0.6816	0.058
H(1C)	0.5749	1.1194	0.6265	0.058
H(2A)	0.7018	0.5226	0.6999	0.049
H(2B)	0.6441	0.4854	0.7871	0.049
H(2C)	0.7385	0.6594	0.7885	0.049
H(3A)	0.4803	0.6026	0.5902	0.069
H(3B)	0.4005	0.7761	0.6237	0.069
H(3C)	0.4260	0.5594	0.6787	0.069
H(4A)	0.4966	0.8169	0.8488	0.035
H(4B)	0.5921	0.9887	0.8512	0.035
H(5A)	0.3753	1.0355	0.7631	0.031
H(5B)	0.4694	1.1931	0.7418	0.031
H(6A)	0.2056	1.1681	0.8835	0.026
H(7A)	0.1746	1.1889	1.0438	0.035
H(8A)	0.1439	0.8351	1.0917	0.040
H(9A)	0.2742	0.6214	1.0047	0.035
H(10A)	0.2973	0.7833	0.8684	0.027
H(13A)	−0.0410	0.9645	0.8321	0.055
H(13B)	−0.1315	0.9486	0.7458	0.055
H(13C)	−0.0734	1.1719	0.7724	0.055
H(14A)	0.0680	1.0189	0.5950	0.042
H(14B)	−0.0206	1.1858	0.6194	0.042
H(16A)	−0.0861	0.6432	0.6458	0.039
H(17A)	−0.2230	0.4559	0.5537	0.048
H(18A)	−0.3057	0.6084	0.4199	0.054
H(19A)	−0.2480	0.9384	0.3749	0.054
H(20A)	−0.1165	1.1311	0.4672	0.043

Table 17. Torsion angles [°] for (-)-**310**.

O(1)–S(1)–N(1)–C(6)	44.42(17)	O(2)–S(1)–N(1)–C(6)	172.91(14)
C(5)–S(1)–N(1)–C(6)	−71.34(16)	C(3)–Si(2)–C(4)–C(5)	−62.20(18)
C(2)–Si(2)–C(4)–C(5)	179.15(14)	C(1)–Si(2)–C(4)–C(5)	57.89(16)
Si(2)–C(4)–C(5)–S(1)	−166.84(10)	O(1)–S(1)–C(5)–C(4)	175.38(14)
O(2)–S(1)–C(5)–C(4)	46.10(17)	N(1)–S(1)–C(5)–C(4)	−68.25(16)
S(1)–N(1)–C(6)–C(7)	−148.33(14)	S(1)–N(1)–C(6)–C(10)	97.77(16)
N(1)–C(6)–C(7)–C(8)	−107.98(19)	C(10)–C(6)–C(7)–C(8)	12.5(2)
C(6)–C(7)–C(8)–C(9)	−1.5(2)	C(11)–O(3)–C(9)–C(8)	96.15(19)
C(11)–O(3)–C(9)–C(10)	−15.3(2)	C(7)–C(8)–C(9)–O(3)	−123.01(19)
C(7)–C(8)–C(9)–C(10)	−10.1(2)	C(11)–N(2)–C(10)–C(6)	−130.59(16)
C(12)–N(2)–C(10)–C(6)	75.9(2)	C(11)–N(2)–C(10)–C(9)	−19.54(19)
C(12)–N(2)–C(10)–C(9)	−173.04(16)	N(1)–C(6)–C(10)–N(2)	−153.15(14)
C(7)–C(6)–C(10)–N(2)	88.80(15)	N(1)–C(6)–C(10)–C(9)	100.22(16)
C(7)–C(6)–C(10)–C(9)	−17.83(17)	O(3)–C(9)–C(10)–N(2)	20.04(18)
C(8)–C(9)–C(10)–N(2)	−97.49(15)	O(3)–C(9)–C(10)–C(6)	134.71(14)
C(8)–C(9)–C(10)–C(6)	17.18(18)	C(9)–O(3)–C(11)–O(4)	−176.8(2)
C(9)–O(3)–C(11)–N(2)	3.2(2)	C(12)–N(2)–C(11)–O(4)	−16.1(3)
C(10)–N(2)–C(11)–O(4)	−168.6(2)	C(12)–N(2)–C(11)–O(3)	164.02(16)
C(10)–N(2)–C(11)–O(3)	11.5(2)	C(13)–N(3)–C(12)–O(5)	−163.8(2)
C(14)–N(3)–C(12)–O(5)	7.8(3)	C(13)–N(3)–C(12)–N(2)	13.5(3)
C(14)–N(3)–C(12)–N(2)	−174.91(18)	C(11)–N(2)–C(12)–O(5)	−117.0(2)
C(10)–N(2)–C(12)–O(5)	33.7(3)	C(11)–N(2)–C(12)–N(3)	65.5(2)
C(10)–N(2)–C(12)–N(3)	−143.79(17)	C(12)–N(3)–C(14)–C(15)	116.89(19)
C(13)–N(3)–C(14)–C(15)	−70.8(2)	N(3)–C(14)–C(15)–C(16)	−21.0(3)
N(3)–C(14)–C(15)–C(20)	161.12(18)	C(20)–C(15)–C(16)–C(17)	−1.1(3)
C(14)–C(15)–C(16)–C(17)	−178.93(18)	C(15)–C(16)–C(17)–C(18)	0.4(3)
C(16)–C(17)–C(18)–C(19)	1.3(3)	C(17)–C(18)–C(19)–C(20)	−2.3(3)
C(18)–C(19)–C(20)–C(15)	1.7(3)	C(16)–C(15)–C(20)–C(19)	0.0(3)
C(14)–C(15)–C(20)–C(19)	177.99(18)		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C16
O3
C11
O4
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C9
C14
C15
C20
C7
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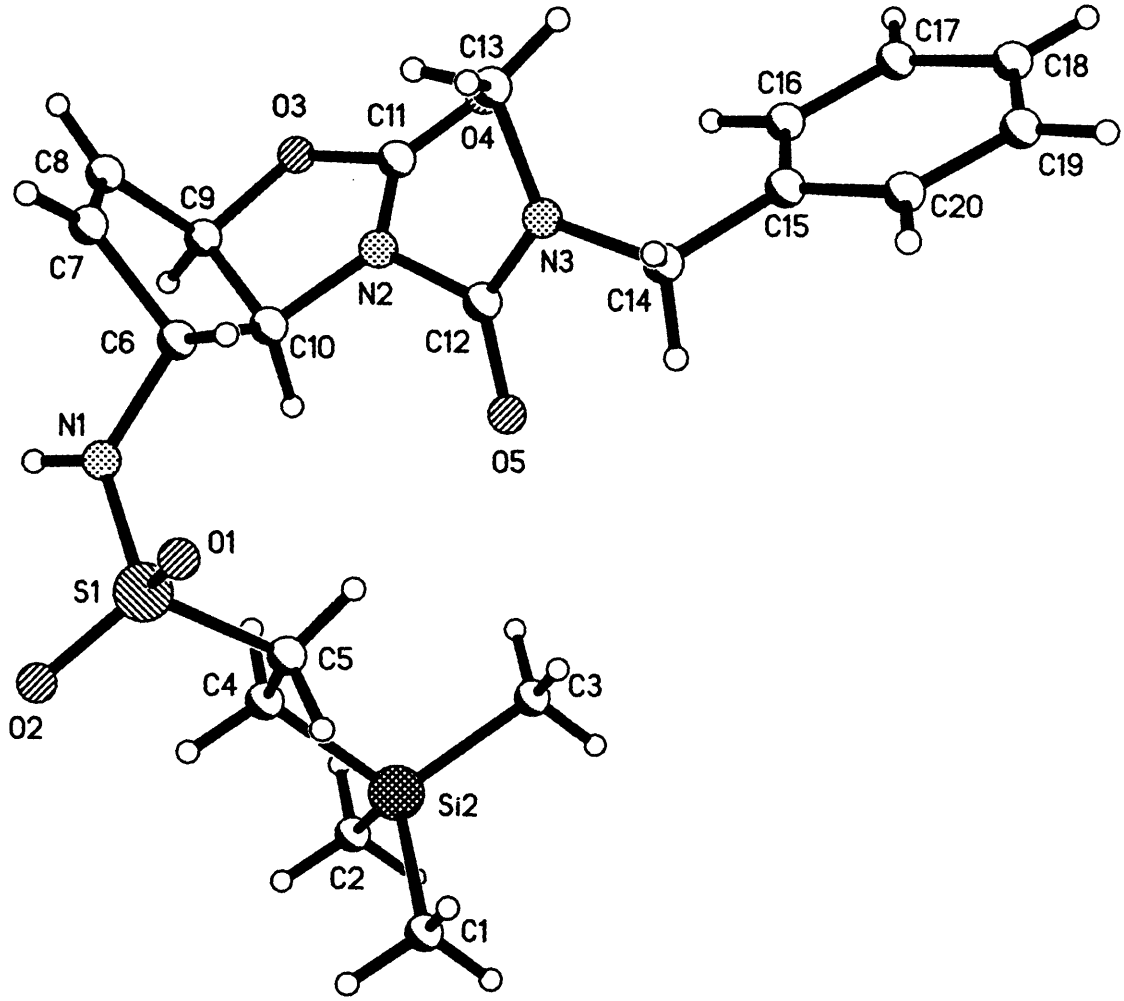
S1
C5
C3
O2
C4
Si2
C2
C1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O3
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C8
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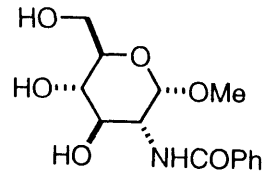
C9
C20
C15
C7
N3
N2
C14
C6
C10
C12
N1
O5
O1
S1
C5
C4
C3
O2
Si2
C2
C1

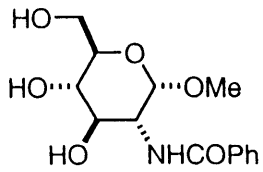
Appendix 2

^{1}H, ^{13}C, 2D-NMR, HRMS and IR spectra of all intermediates discussed in this thesis

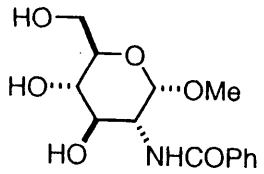
I-md-5
DMSO, 298 K

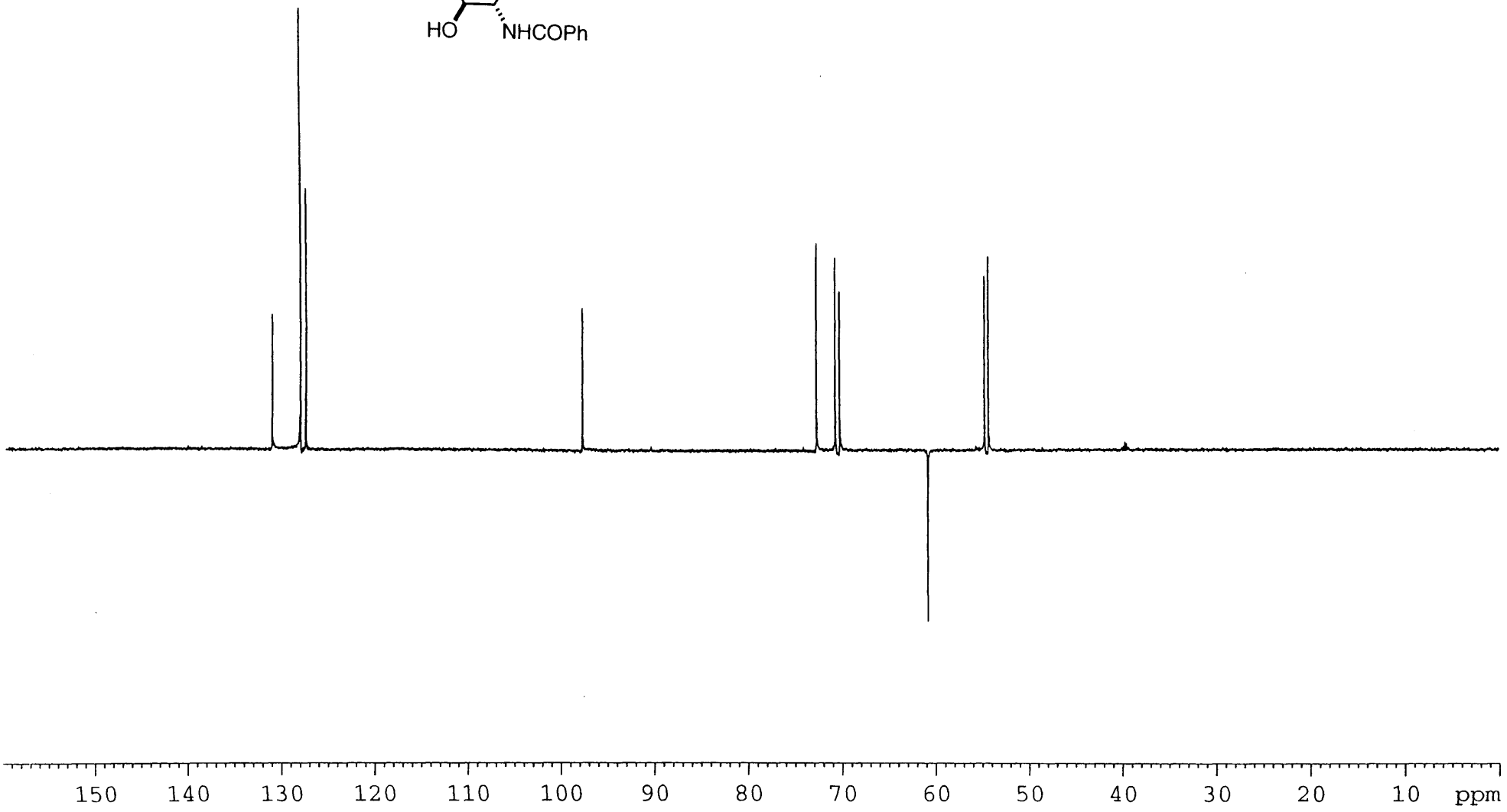


I-md-5
DMSO, 298 K

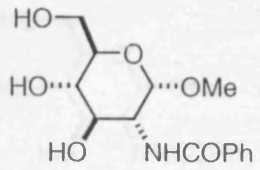


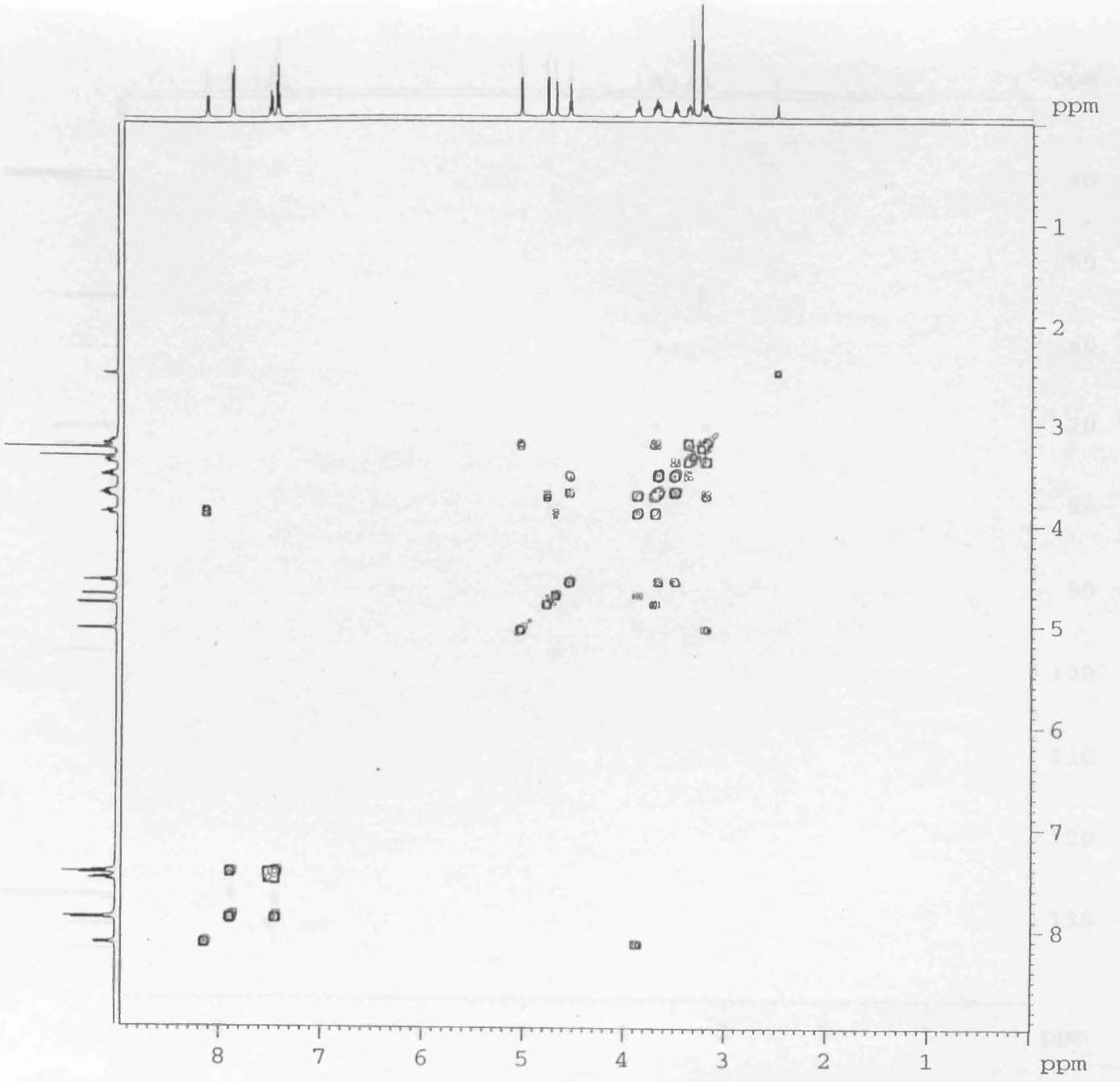
I-md-5
DMSO, 298 K



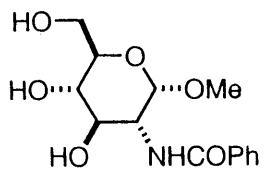


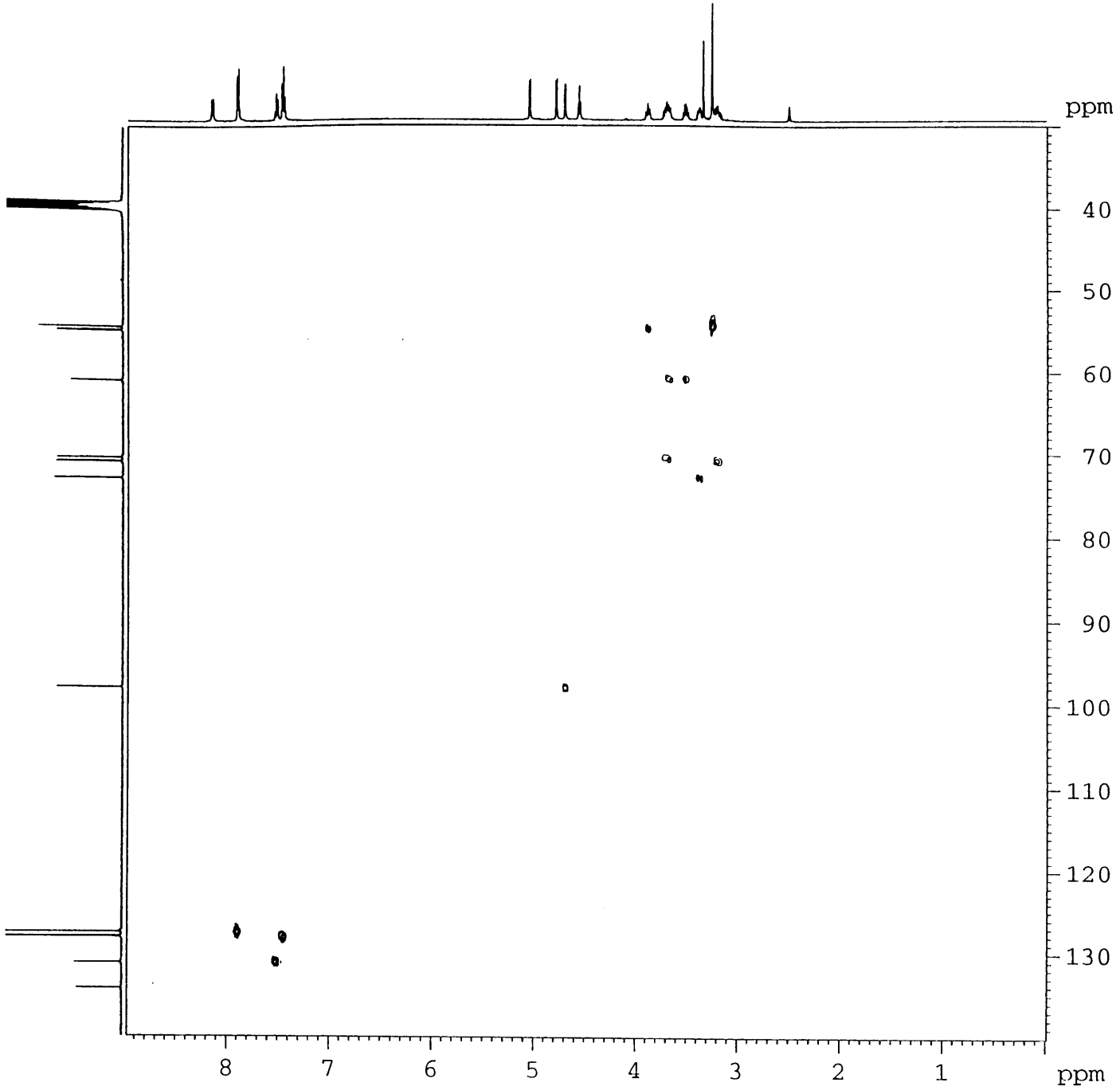
I-md-5
DMSO, 298 K
COSY

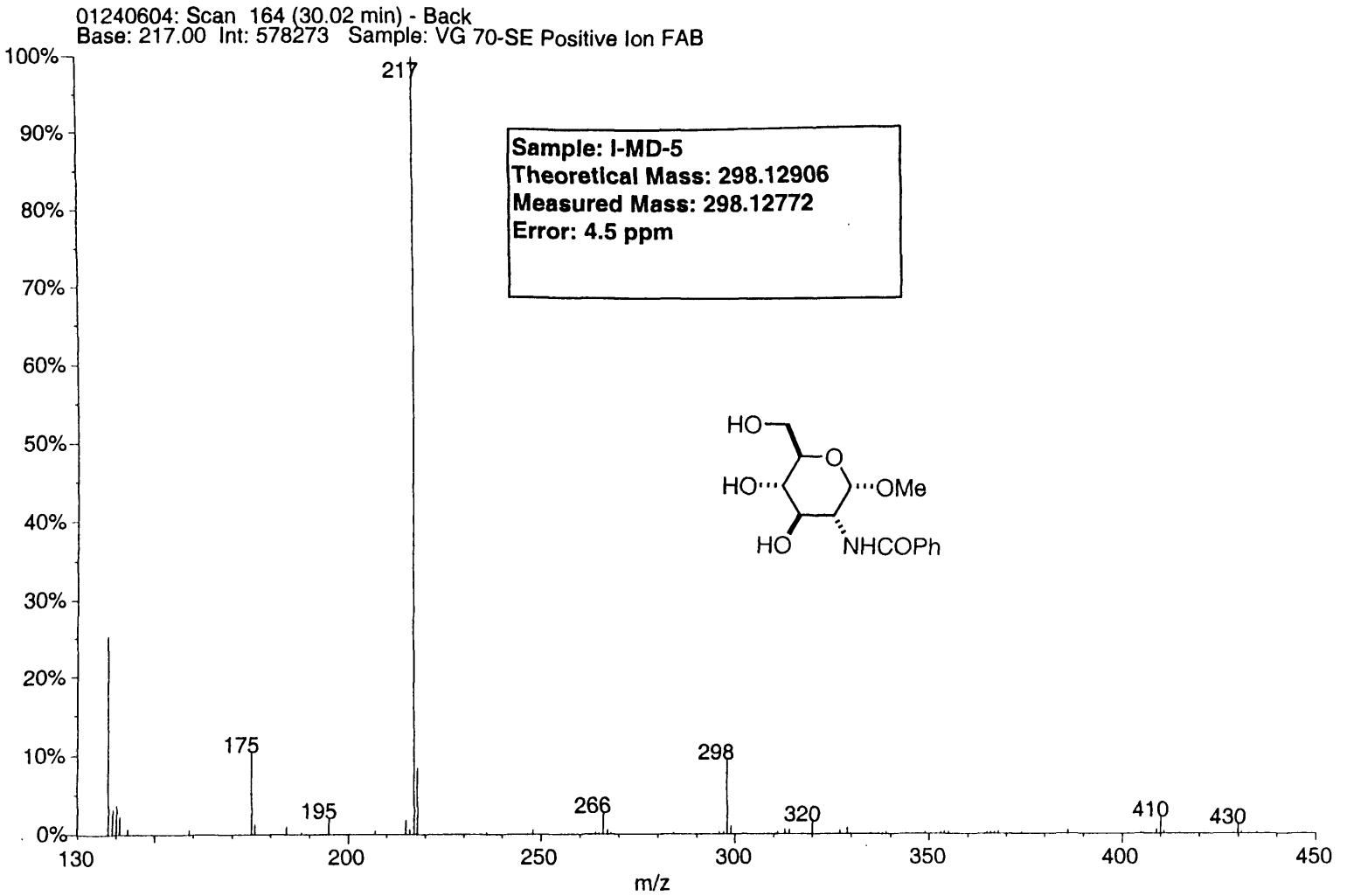




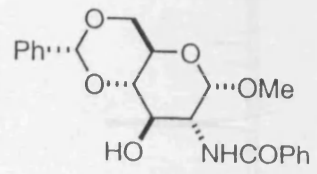
I-md-5
DMSO, 298 K
HMQC



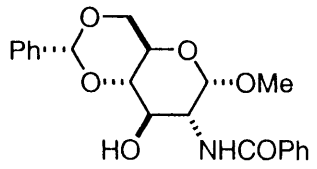


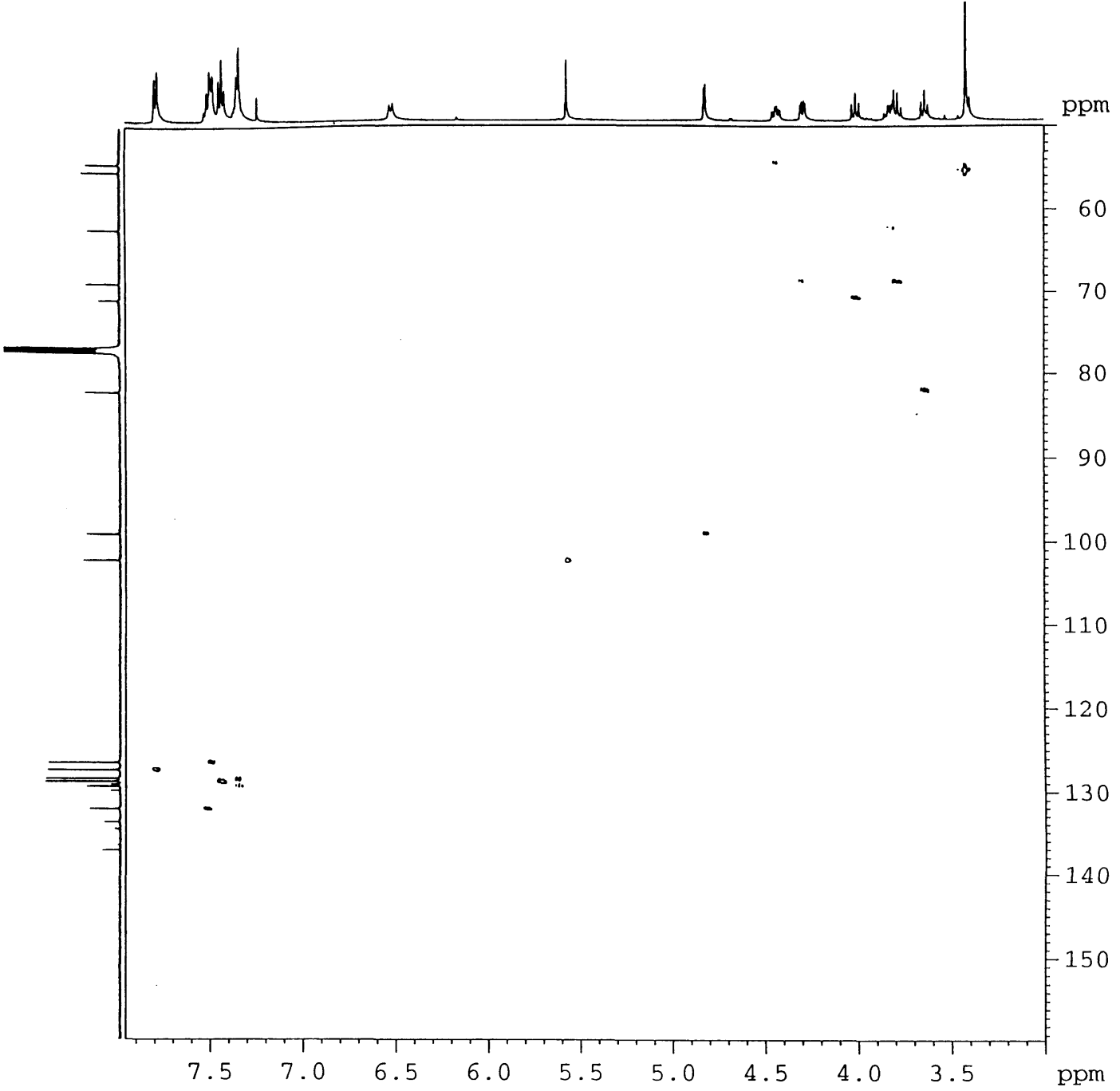

01240604: Scan 164 (30.02 min) - Back
Base: 217.00 Int: 578273 Sample: VG 70-SE Positive Ion FAB
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
217
175
195
266
298
320
410
430
130
200
250
300
350
400
450
m/z
Sample: I-MD-5
Theoretical Mass: 298.12906
Measured Mass: 298.12772
Error: 4.5 ppm
HO
O
HO
OMe
HO
NHCOPh

I-md-37
CDCl3, 298 K

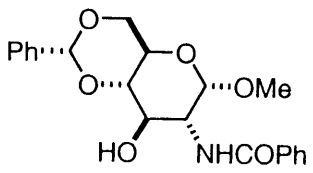


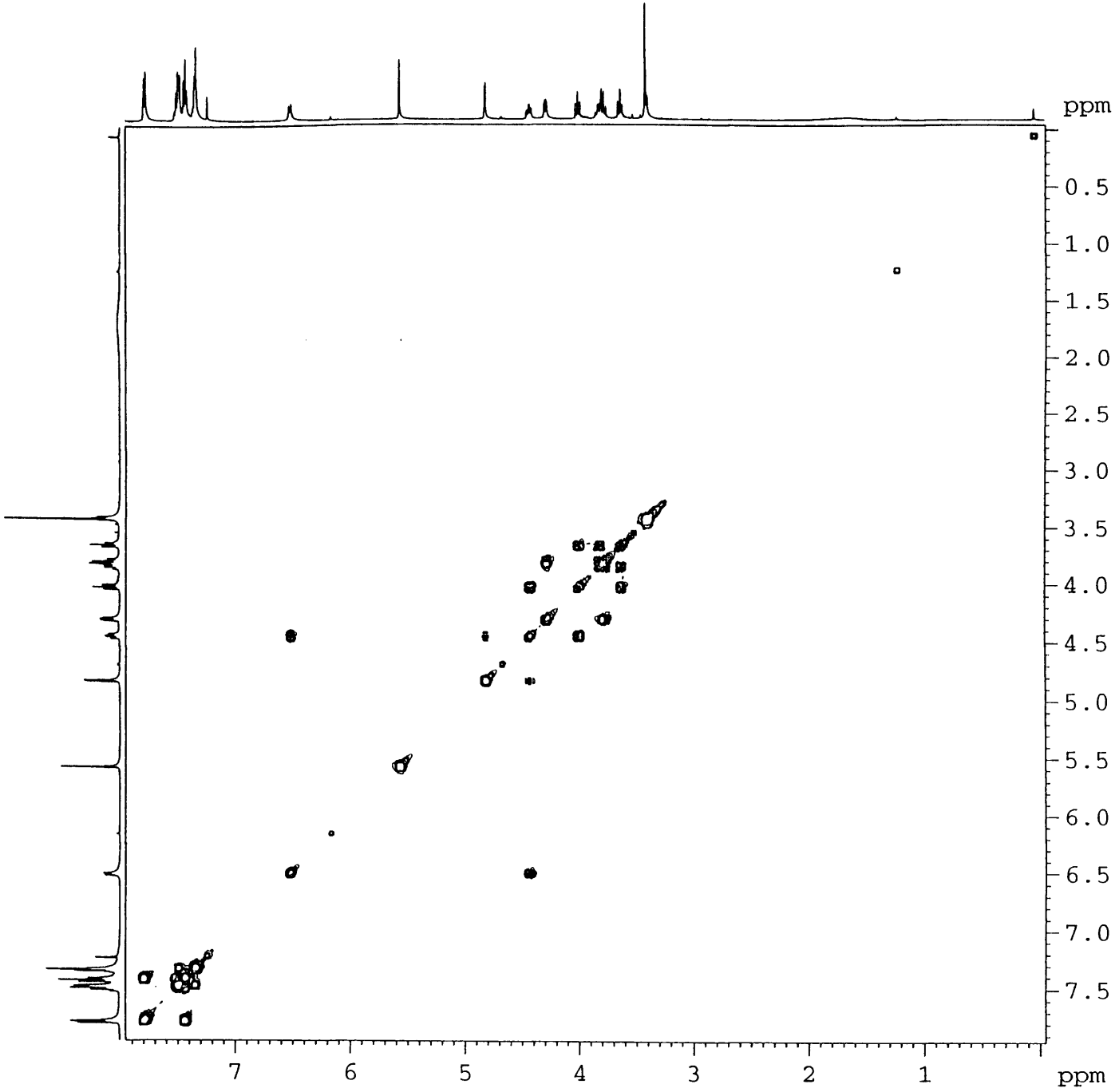
I-md-37
CDCl3, 298 K
HMQC

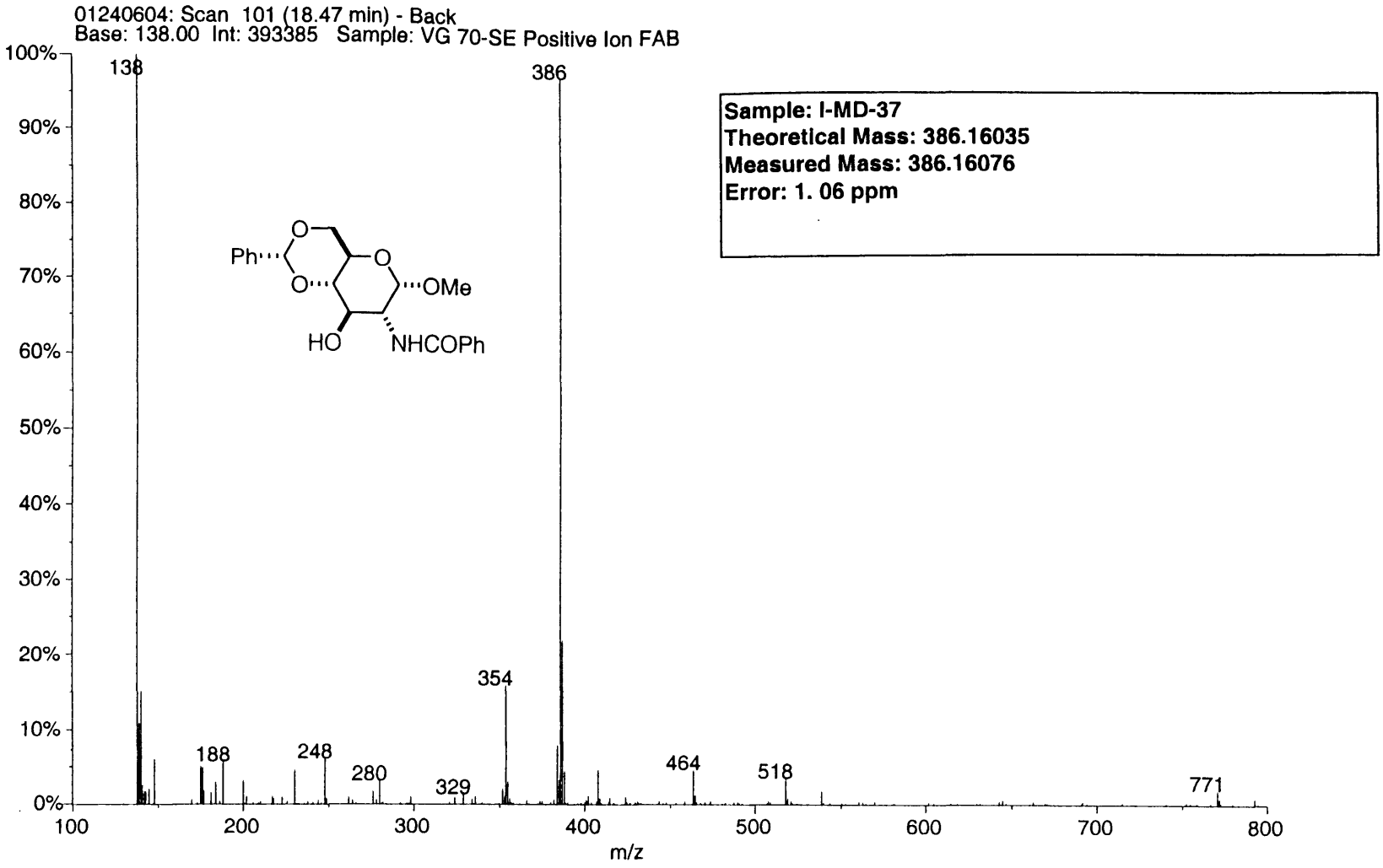




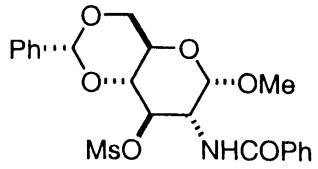
I-md-37
CDC13, 298 K
COSY



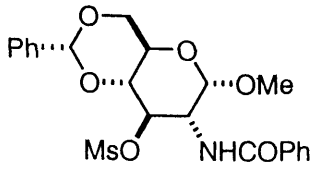


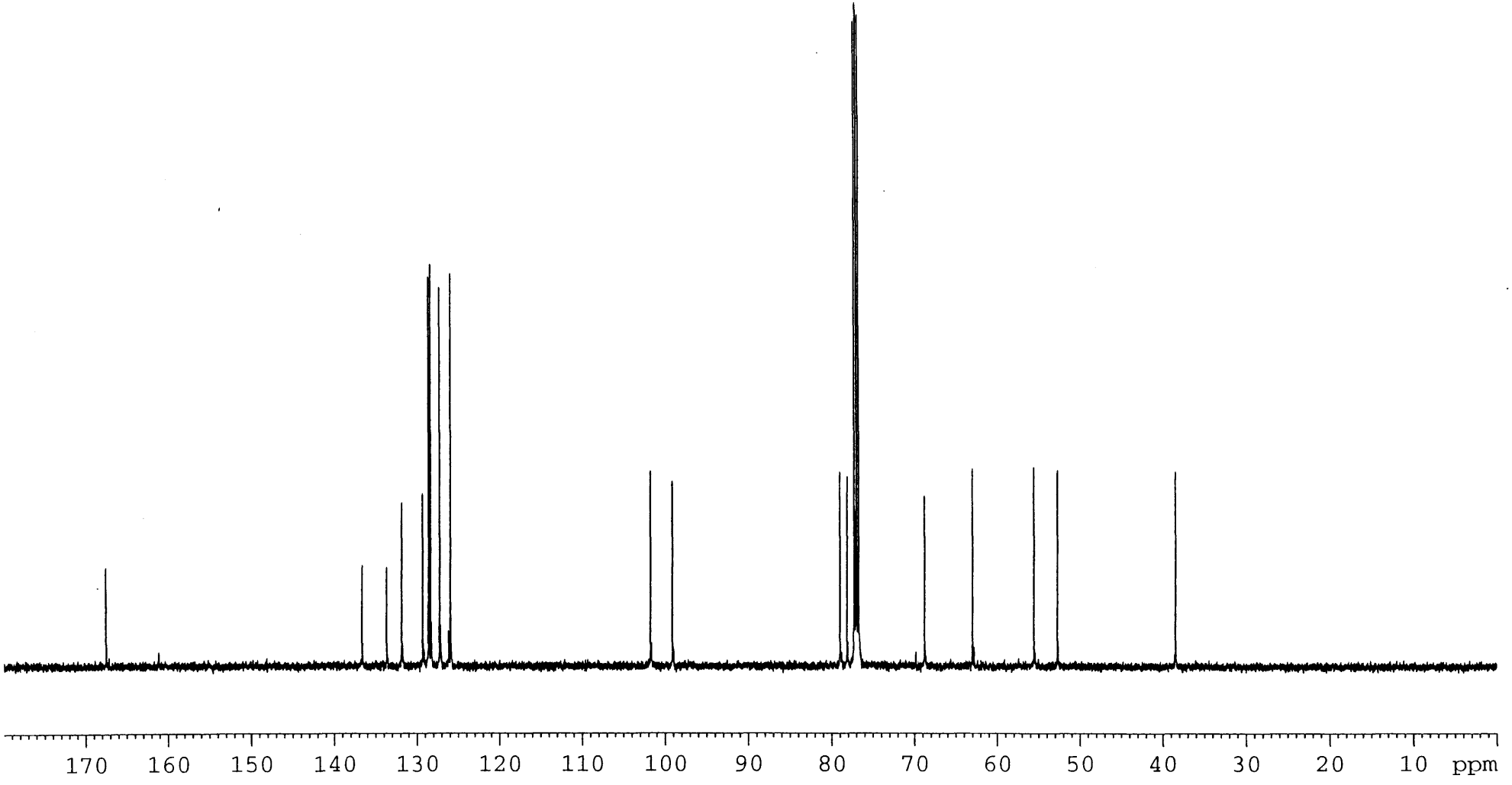

01240604: Scan 101 (18.47 min) - Back
Base: 138.00 Int: 393385 Sample: VG 70-SE Positive Ion FAB
Sample: I-MD-37
Theoretical Mass: 386.16035
Measured Mass: 386.16076
Error: 1. 06 ppm
Ph
OMe
HO
NHCOPh
138
386
354
188
248
280
329
464
518
771
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
100
200
300
400
500
600
700
800
m/z

I-md-18
CDCl3, 298 K

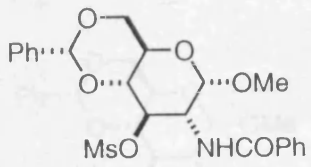


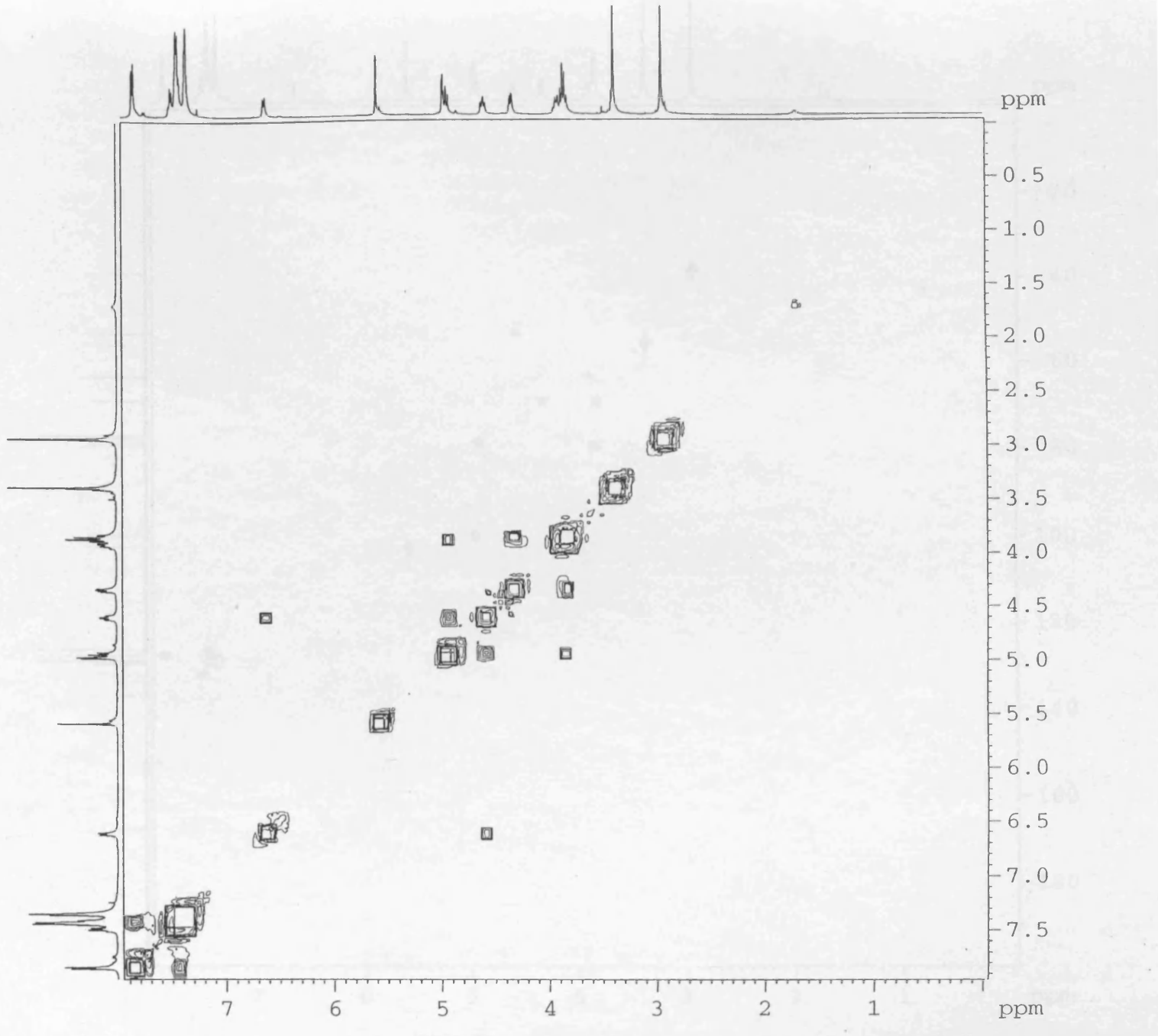
I-md-18
CDCl3, 298 K



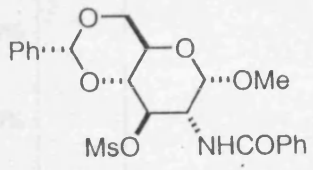


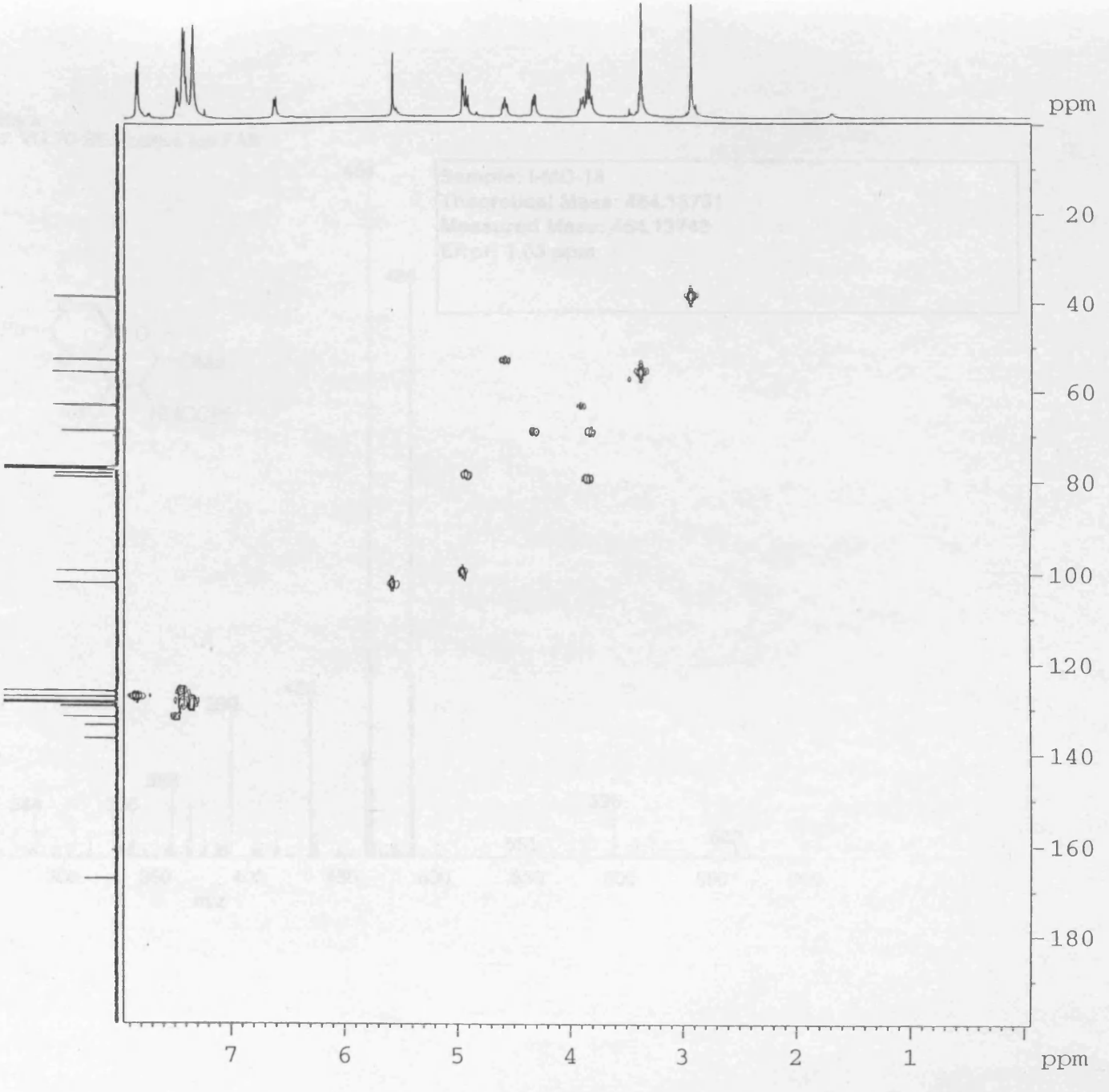
I-md-18
CDCl3, 298 K
COSY

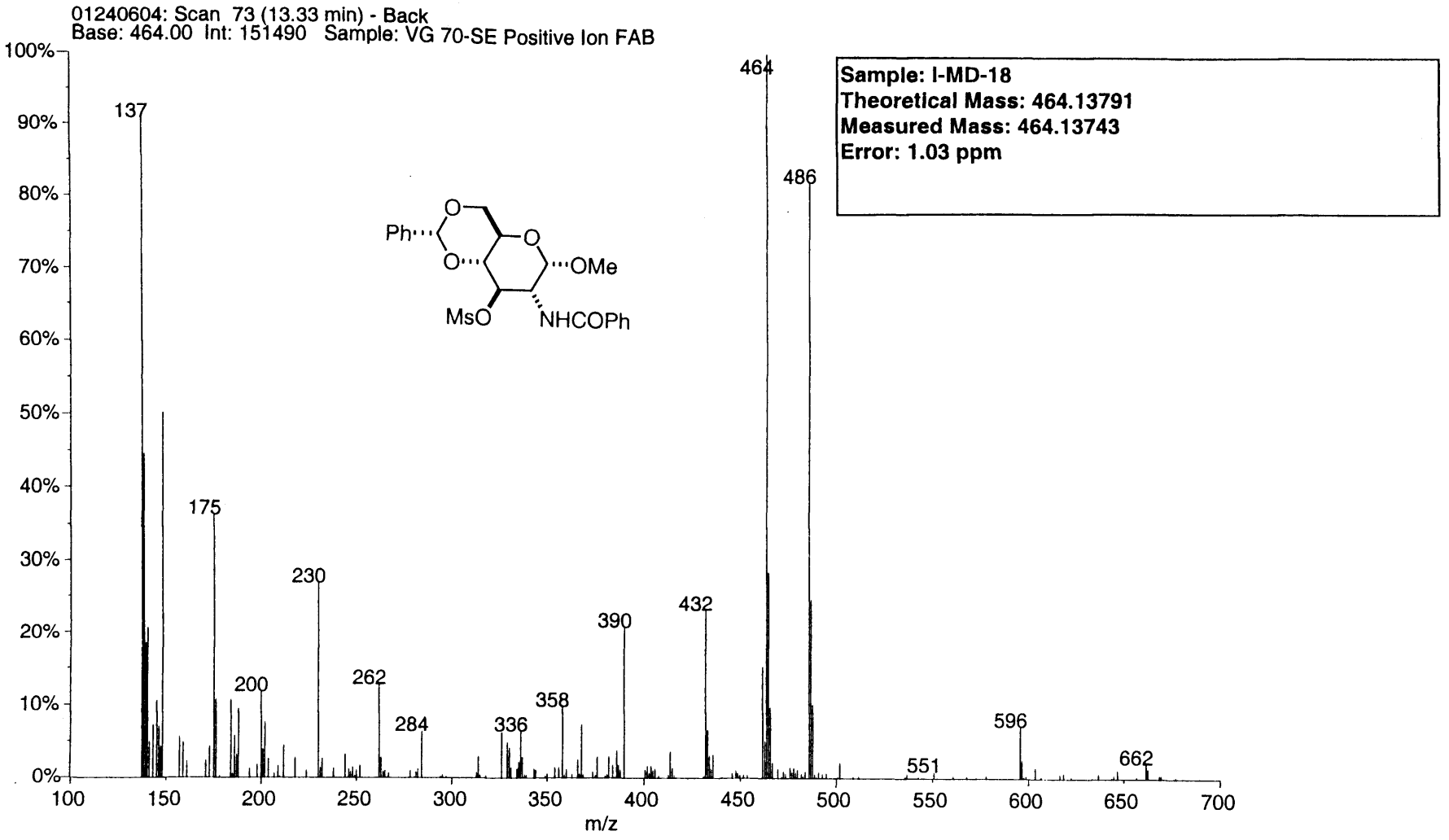




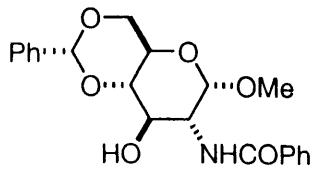
I-md-18
CDCl3, 298 K
HMQC



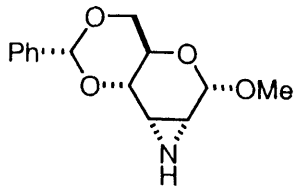



01240604: Scan 73 (13.33 min) - Back
Base: 464.00 Int: 151490 Sample: VG 70-SE Positive Ion FAB
Sample: I-MD-18
Theoretical Mass: 464.13791
Measured Mass: 464.13743
Error: 1.03 ppm
Ph
OMe
MsO
NHCOPh
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
137
175
200
230
262
284
336
358
390
432
464
486
551
596
662
100
150
200
250
300
350
400
450
500
550
600
650
700
m/z

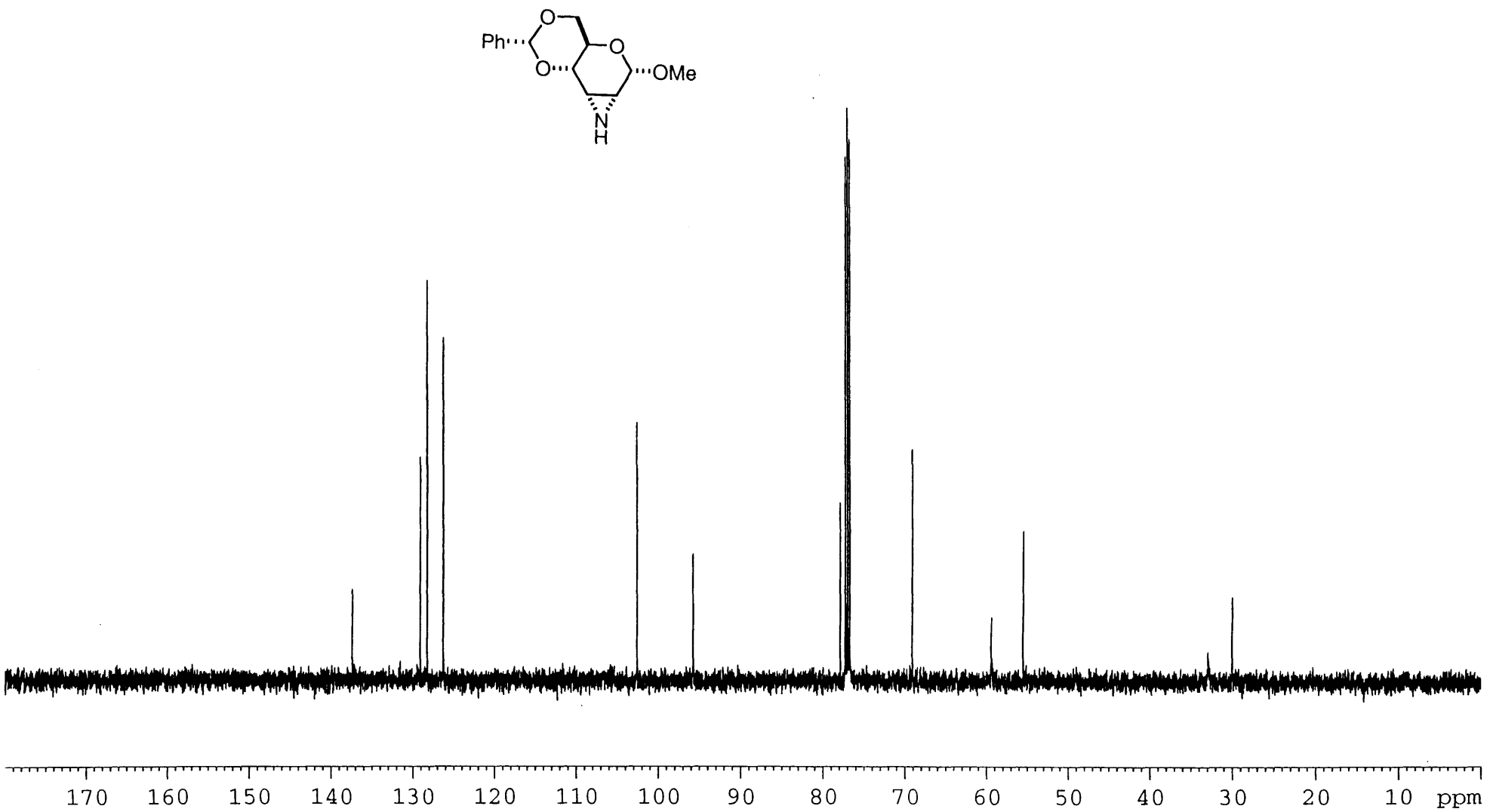
I-md-37
CDCl3, 298 K

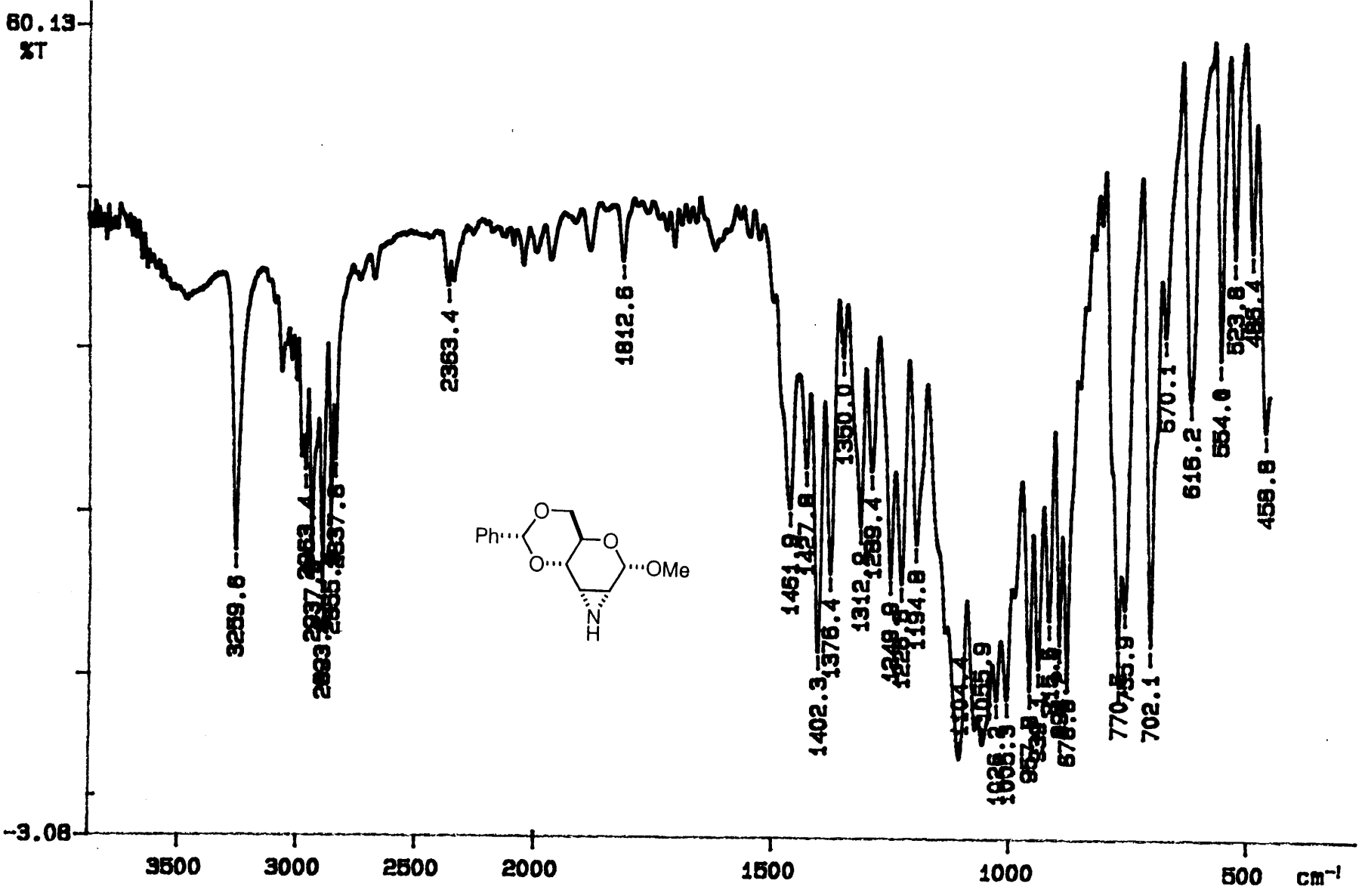


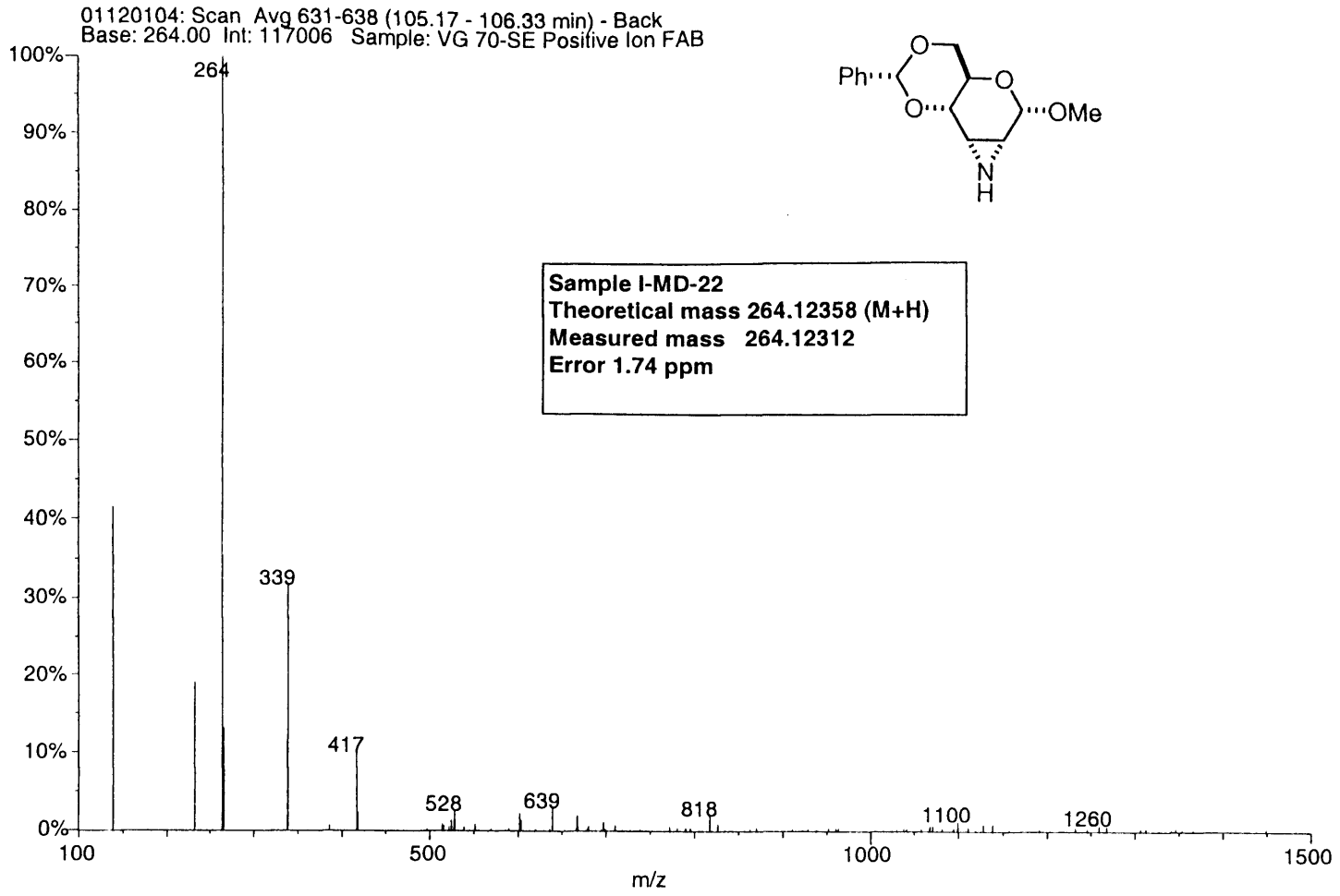
I-md-22
CDCl3, 298 K



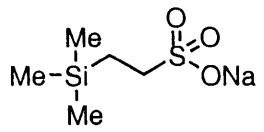
I-md-22
CDCl3, 298 K



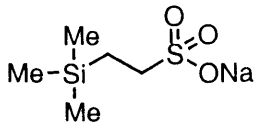

60.13
%T
-3.08
3500
3000
2500
2000
1500
1000
500
cm-1
3239.6
2363.4
1812.6
1461.8
1402.3
1376.4
1350.0
1312.8
1194.8
770.5
702.1
670.1
616.2
554.0
523.8
459.8
Ph
O
O
O
OMe
N
H


01120104: Scan Avg 631-638 (105.17 - 106.33 min) - Back
Base: 264.00 Int: 117006 Sample: VG 70-SE Positive Ion FAB
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
264
339
417
528
639
818
1100
1260
100
500
1000
1500
m/z
Ph
O
O
O
OMe
N
H
Sample I-MD-22
Theoretical mass 264.12358 (M+H)
Measured mass 264.12312
Error 1.74 ppm

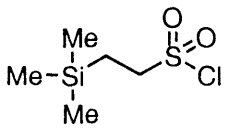
I-md-84
MeOD, 298 K



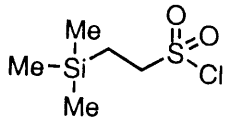
I-md-84
MeOD, 298 K

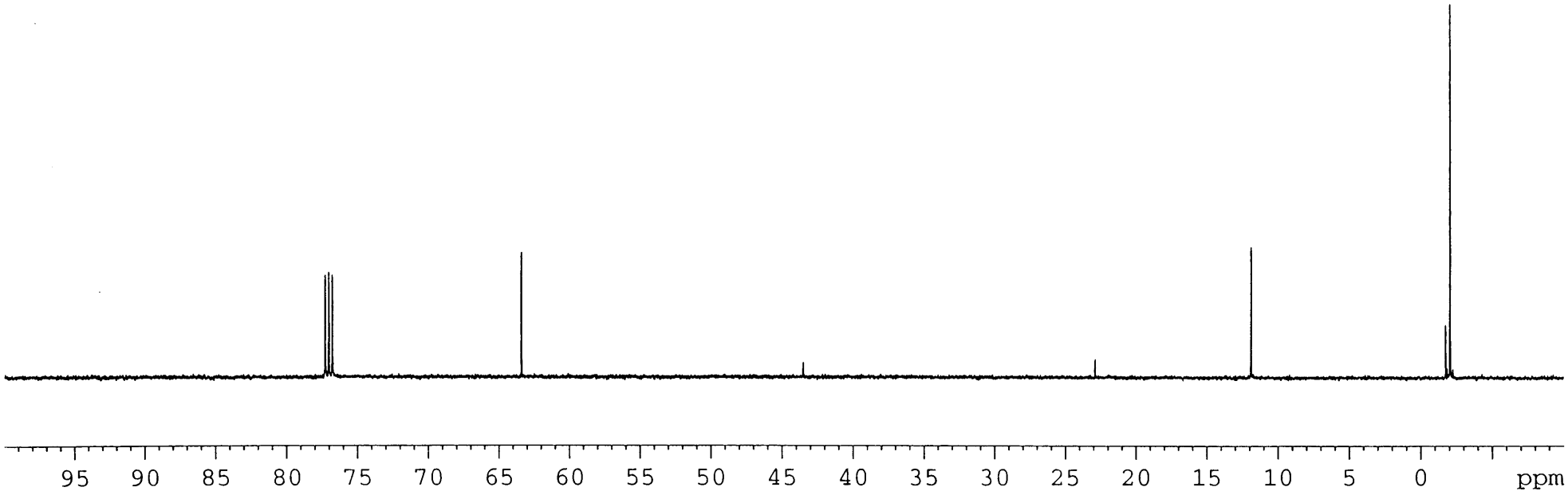


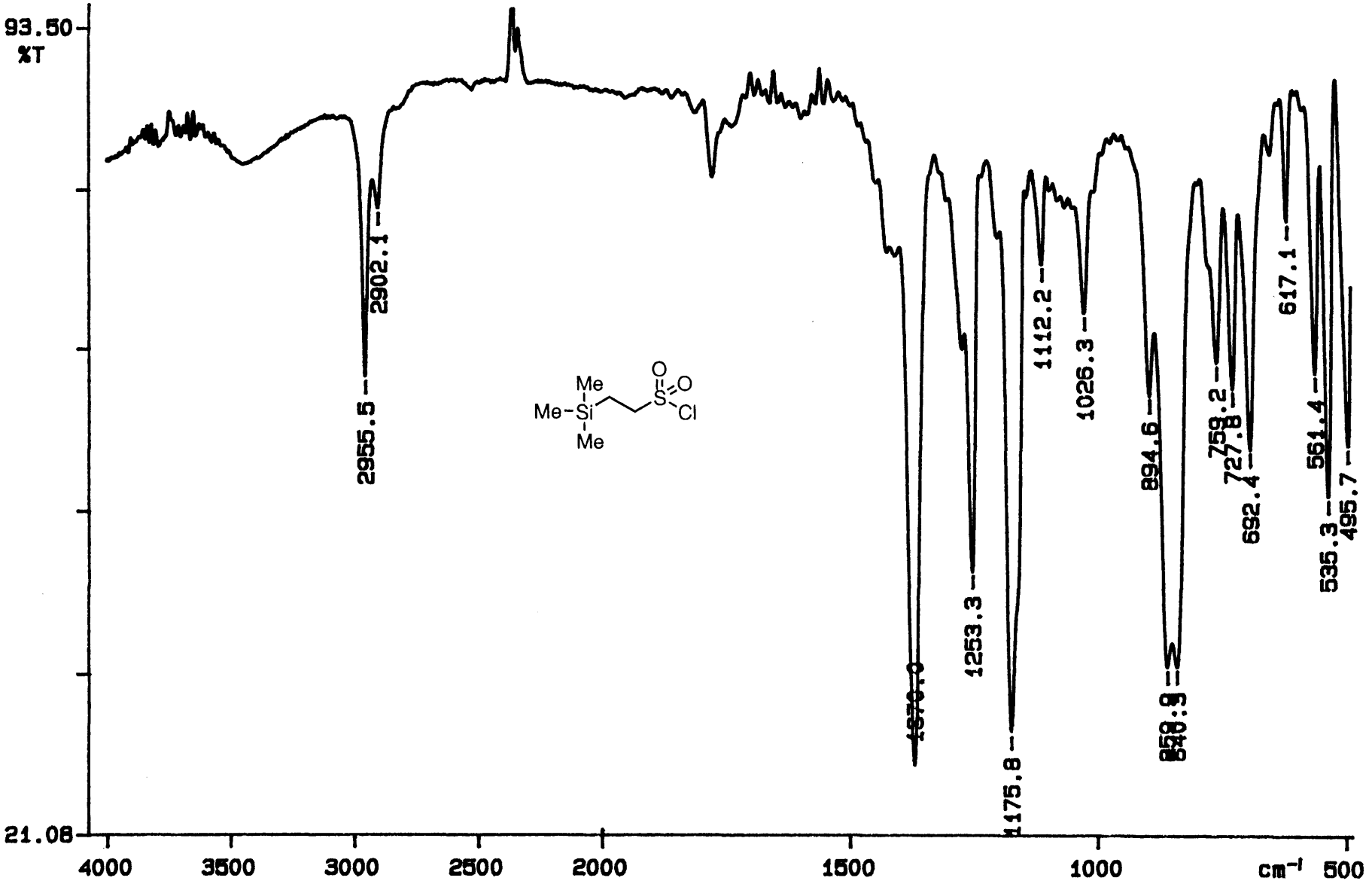
IV-md-140
CDCl3, 298 K



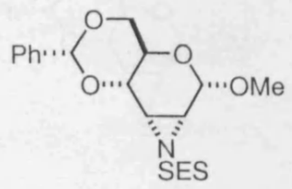
IV-md-140
CDCl3, 298 K



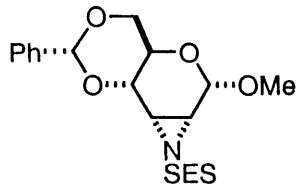


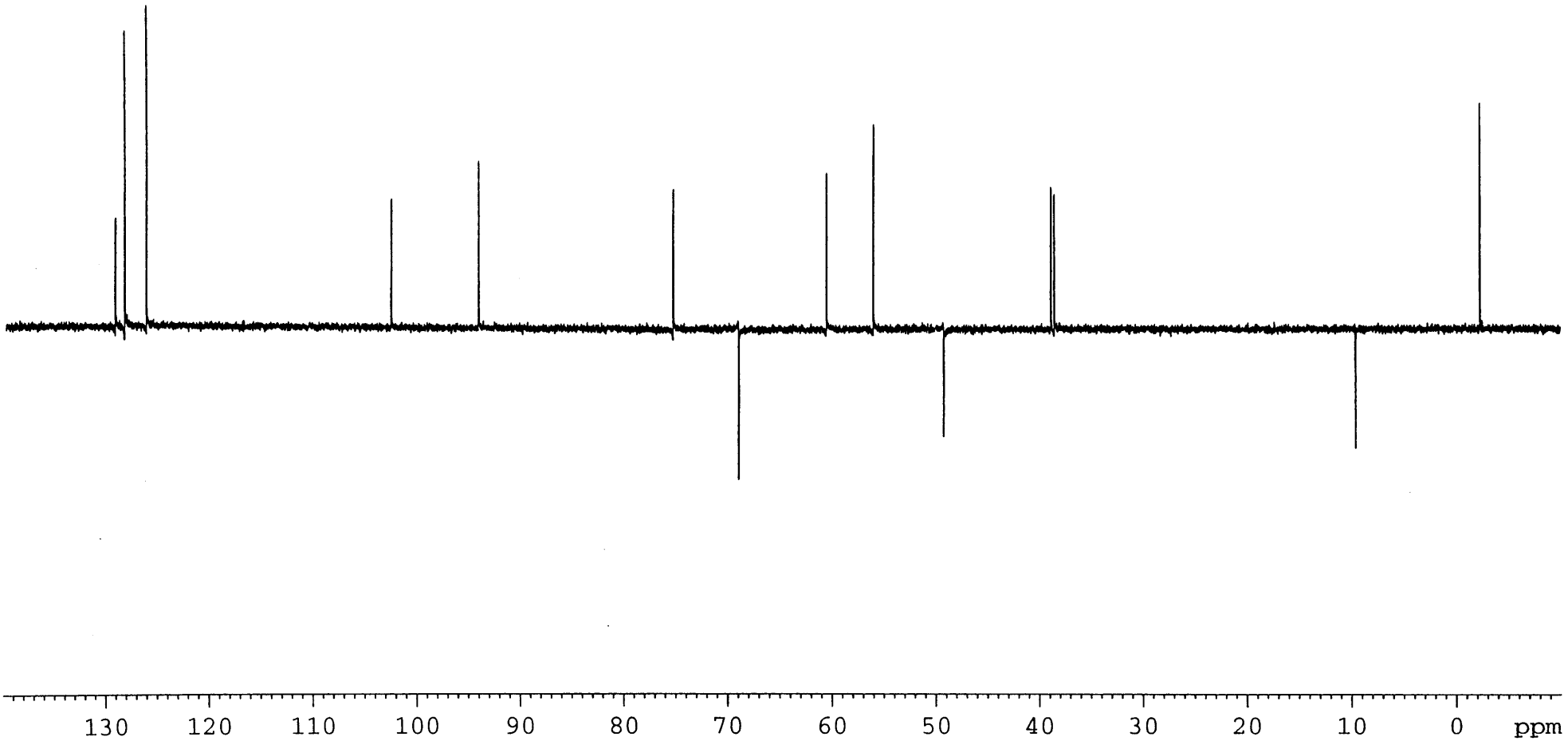

93.50
%T
21.08
2955.5
2902.1
1370.0
1253.3
1175.8
1112.2
1026.3
894.6
759.2
727.8
692.4
617.1
561.4
535.3
495.7
Me
Me-Si
Me
O
S
O
Cl
4000
3500
3000
2500
2000
1500
1000
cm-1
500

I-md-135
CDCl3, 298 K

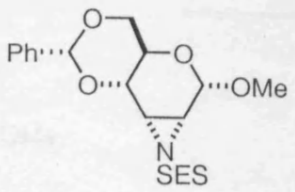


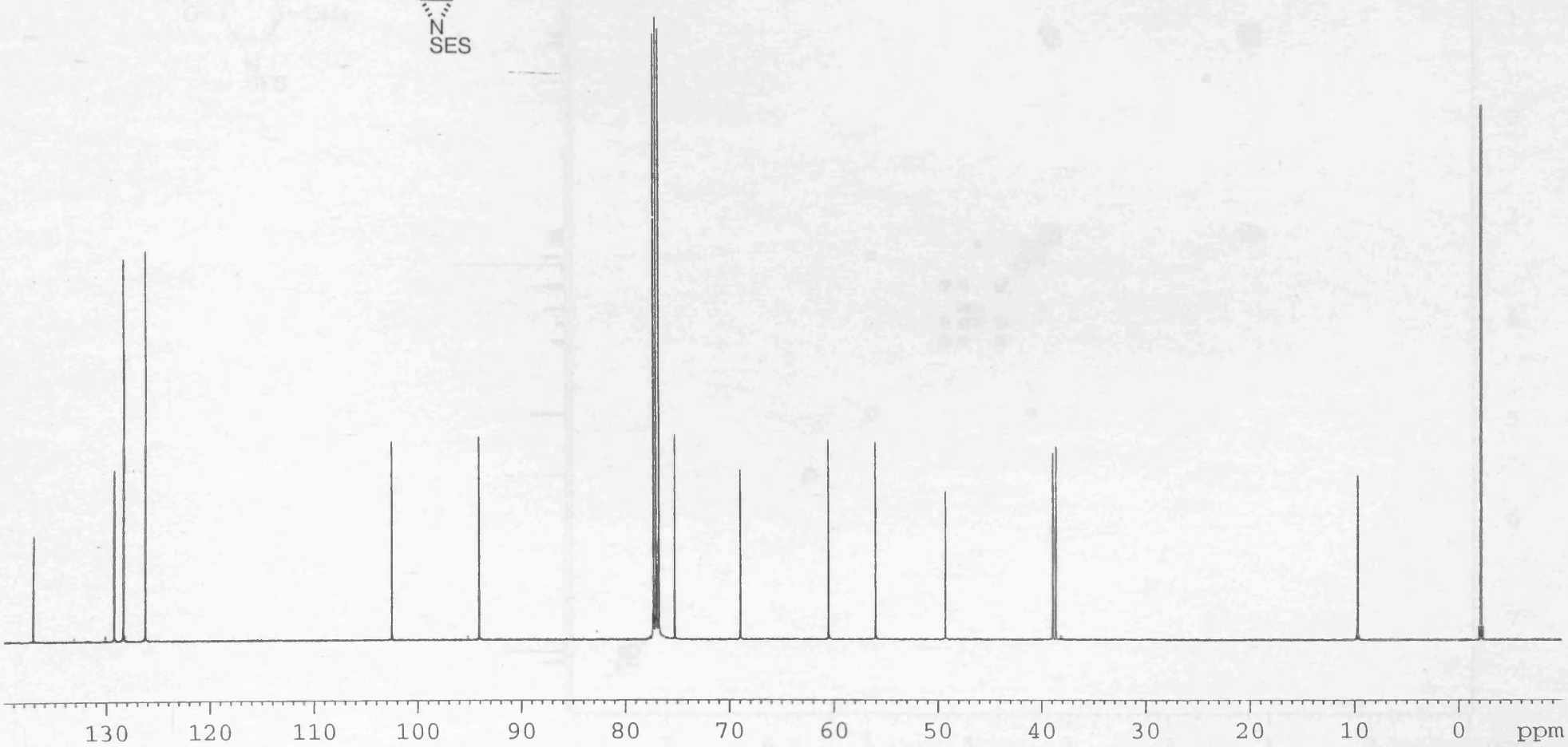
I-md-135
CDCl3, 298 K
DEPT



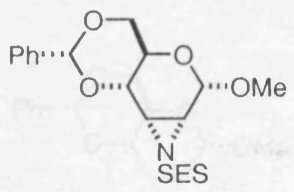


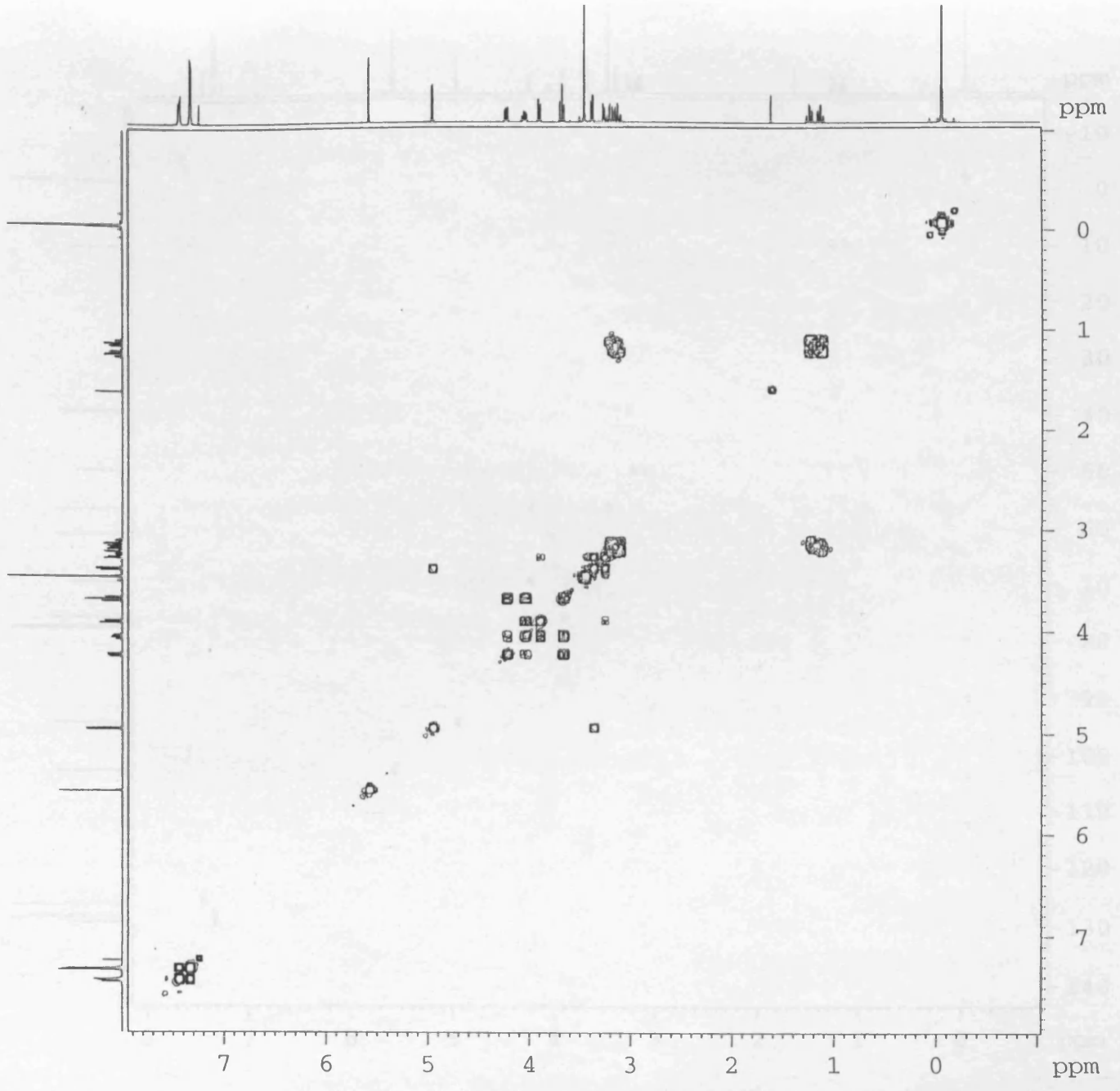
I-md-135
CDCl3, 298 K



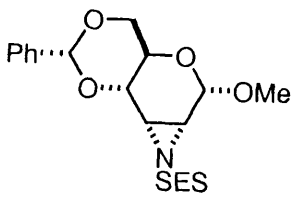


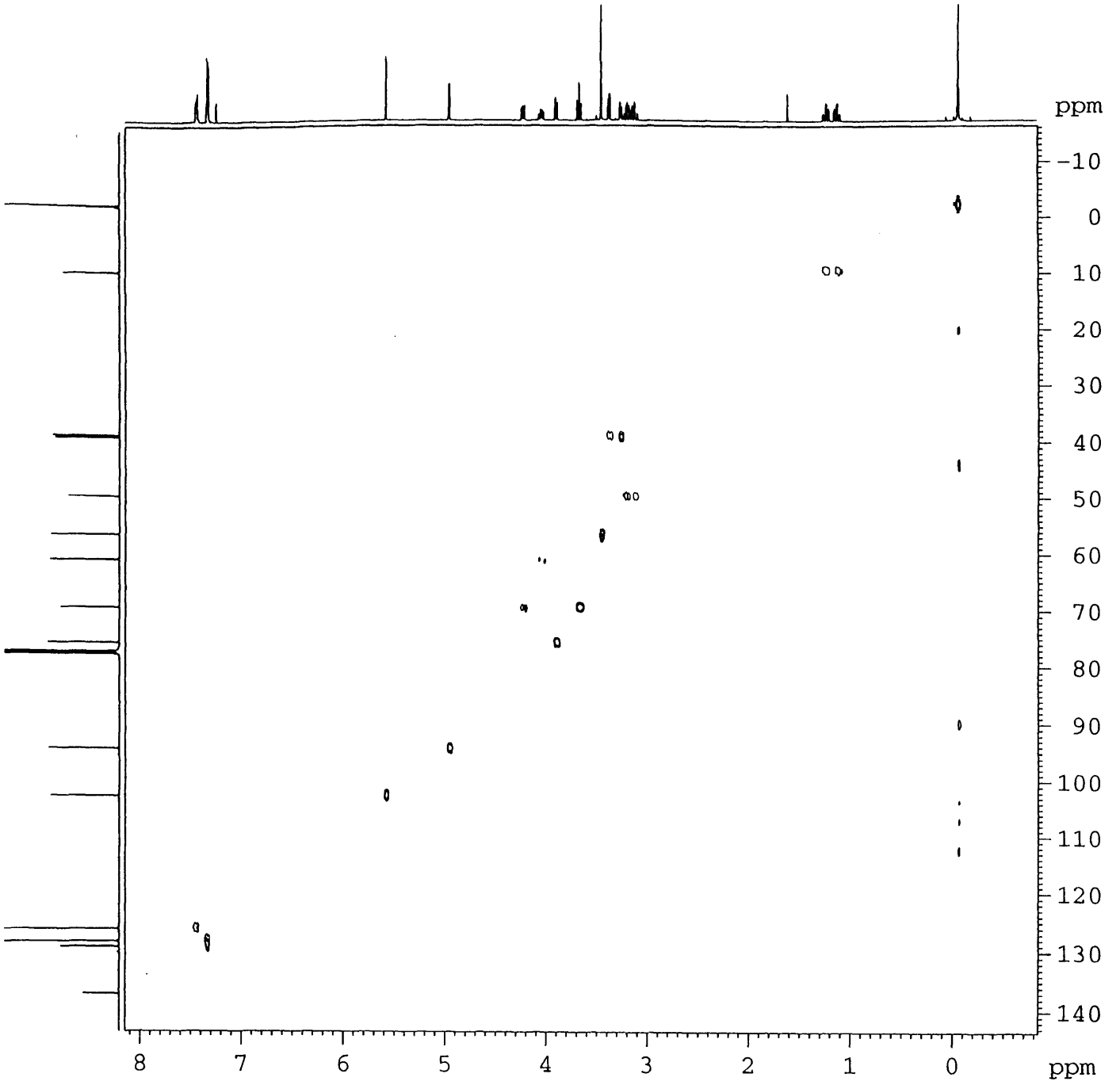
I-md-135
CDC13, 298 K
COSY

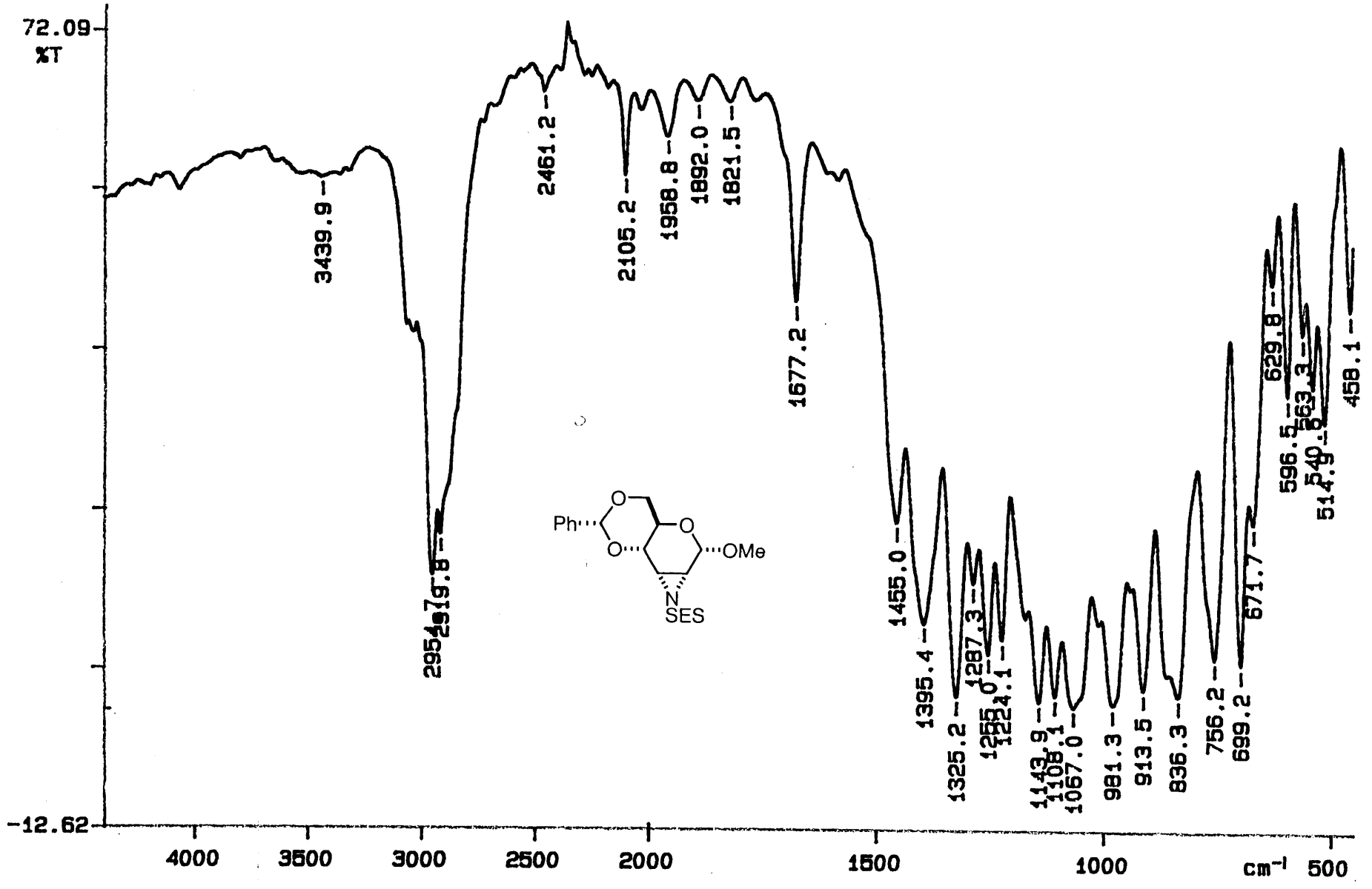




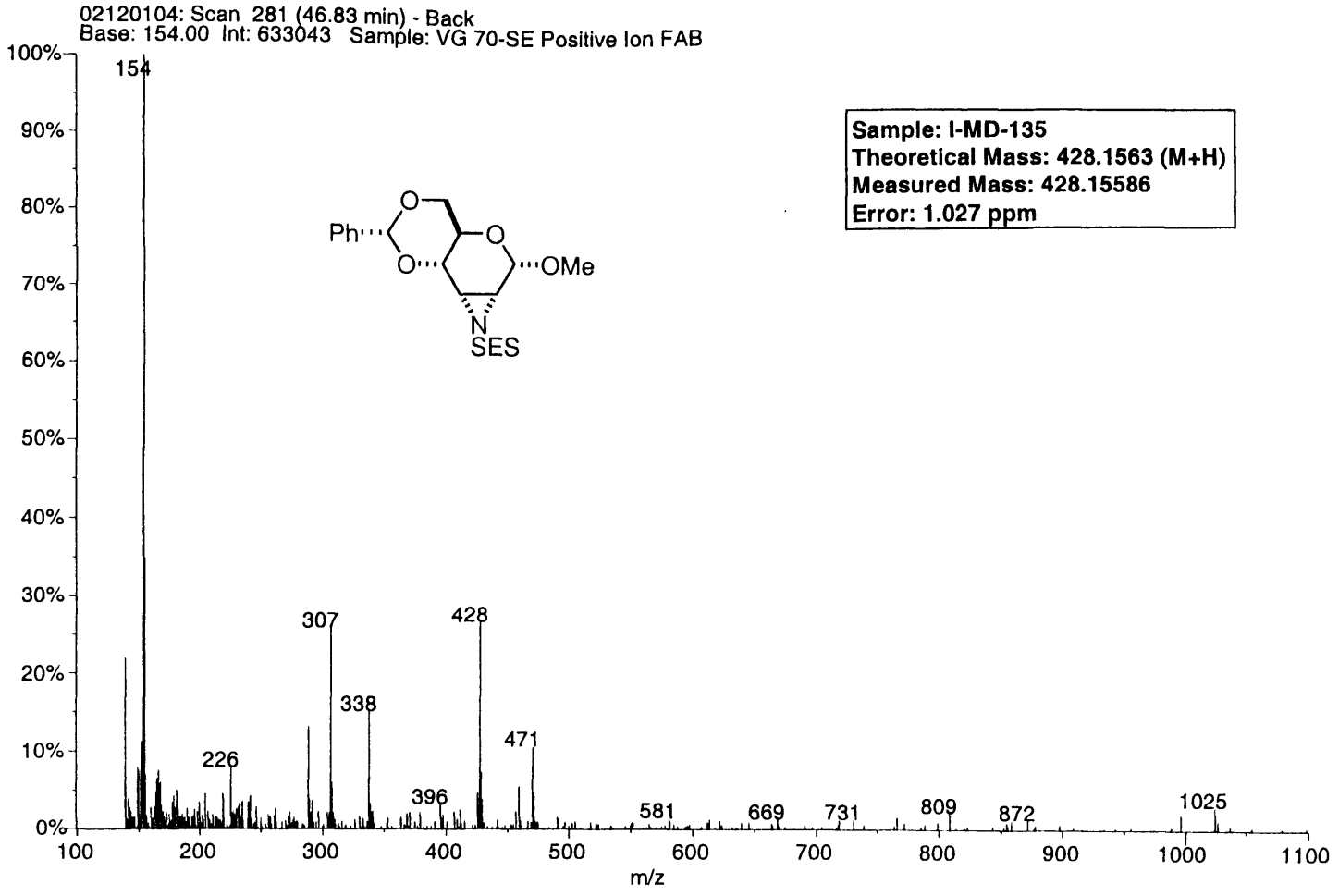
I-md-135
CDCl3, 298 K
HMQC



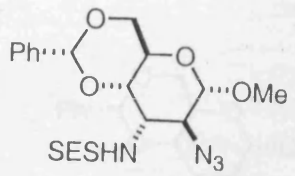




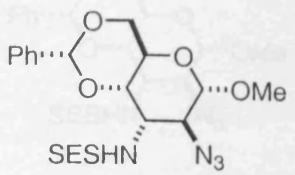
02/05/03 09: 12
X: 16 scans, 16.0cm-1

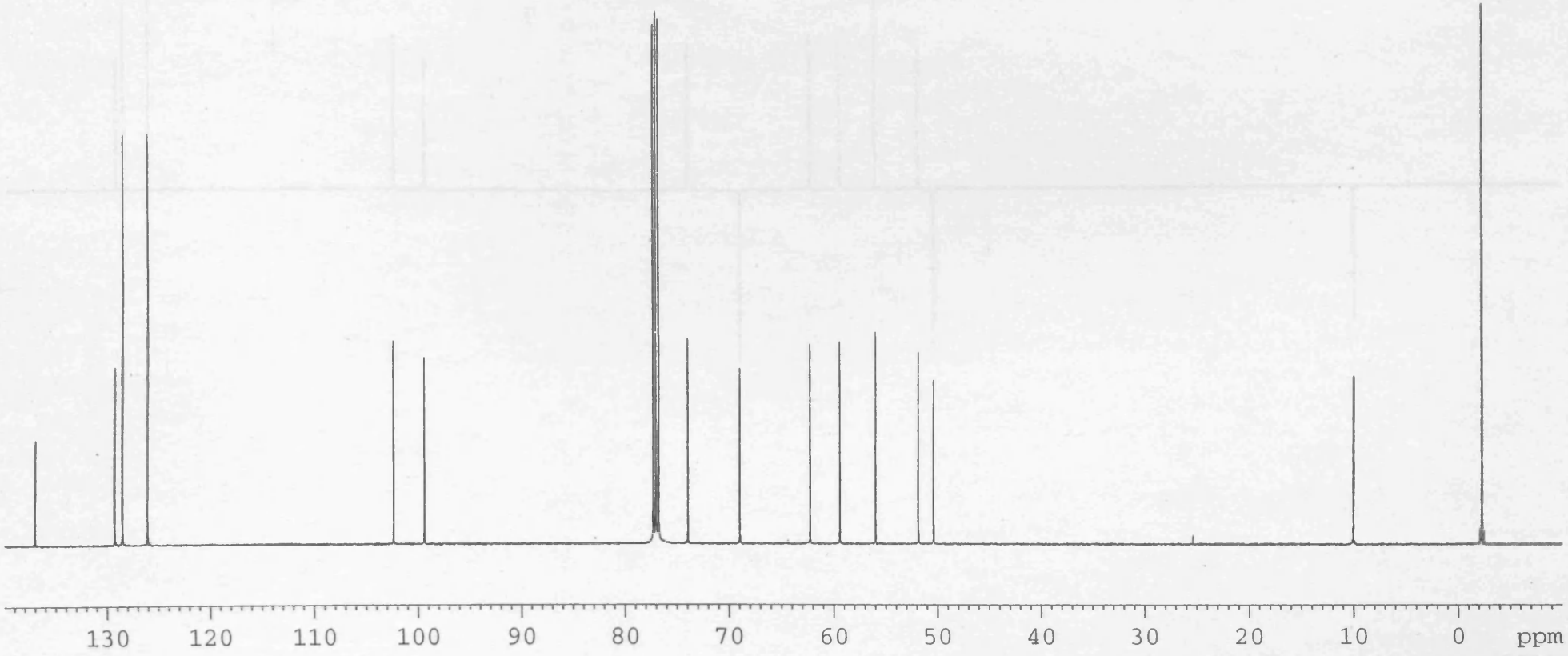

02120104: Scan 281 (46.83 min) - Back
Base: 154.00 Int: 633043 Sample: VG 70-SE Positive Ion FAB
Sample: I-MD-135
Theoretical Mass: 428.1563 (M+H)
Measured Mass: 428.15586
Error: 1.027 ppm
Ph
O
O
O
OMe
N
SES
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
154
307
428
338
471
226
396
581
669
731
809
872
1025
100
200
300
400
500
600
700
800
900
1000
1100
m/z

I-md-100
CDCl3, 298 K

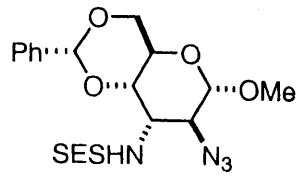


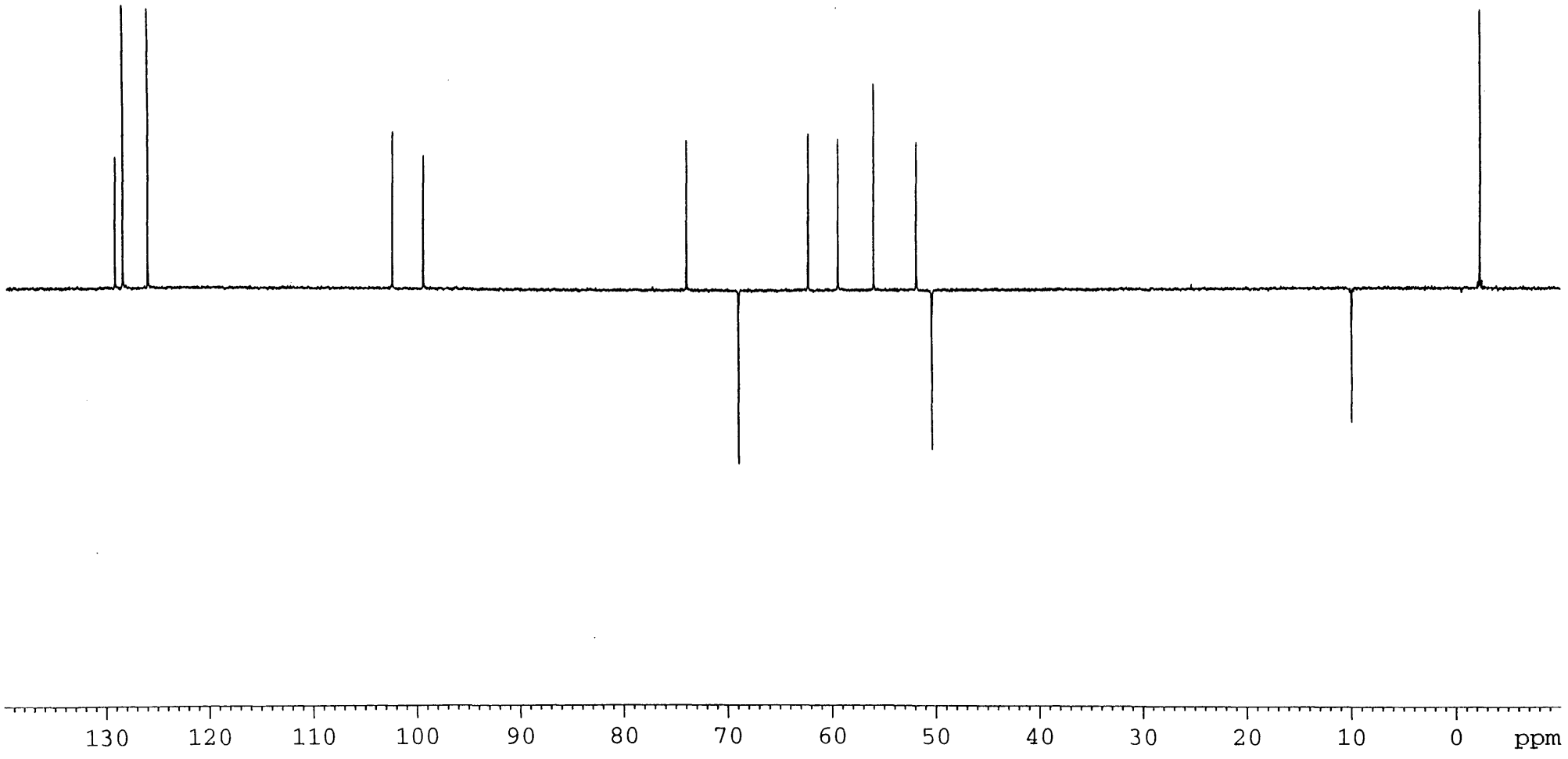
I-md-100
CDCl3, 298 K



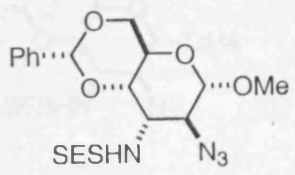


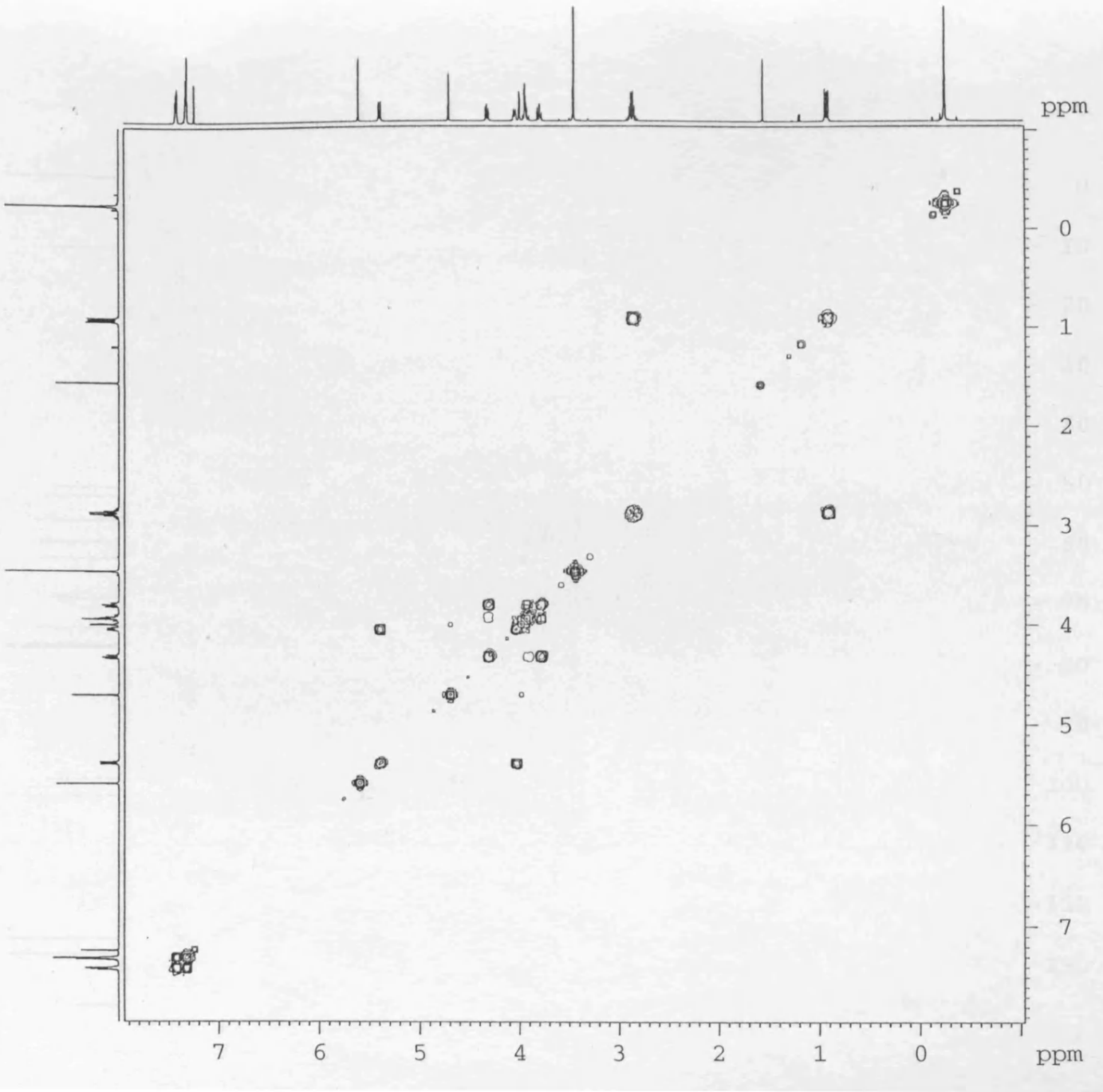
I-md-100
CDCl3, 298 K
DEPT



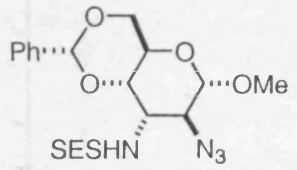


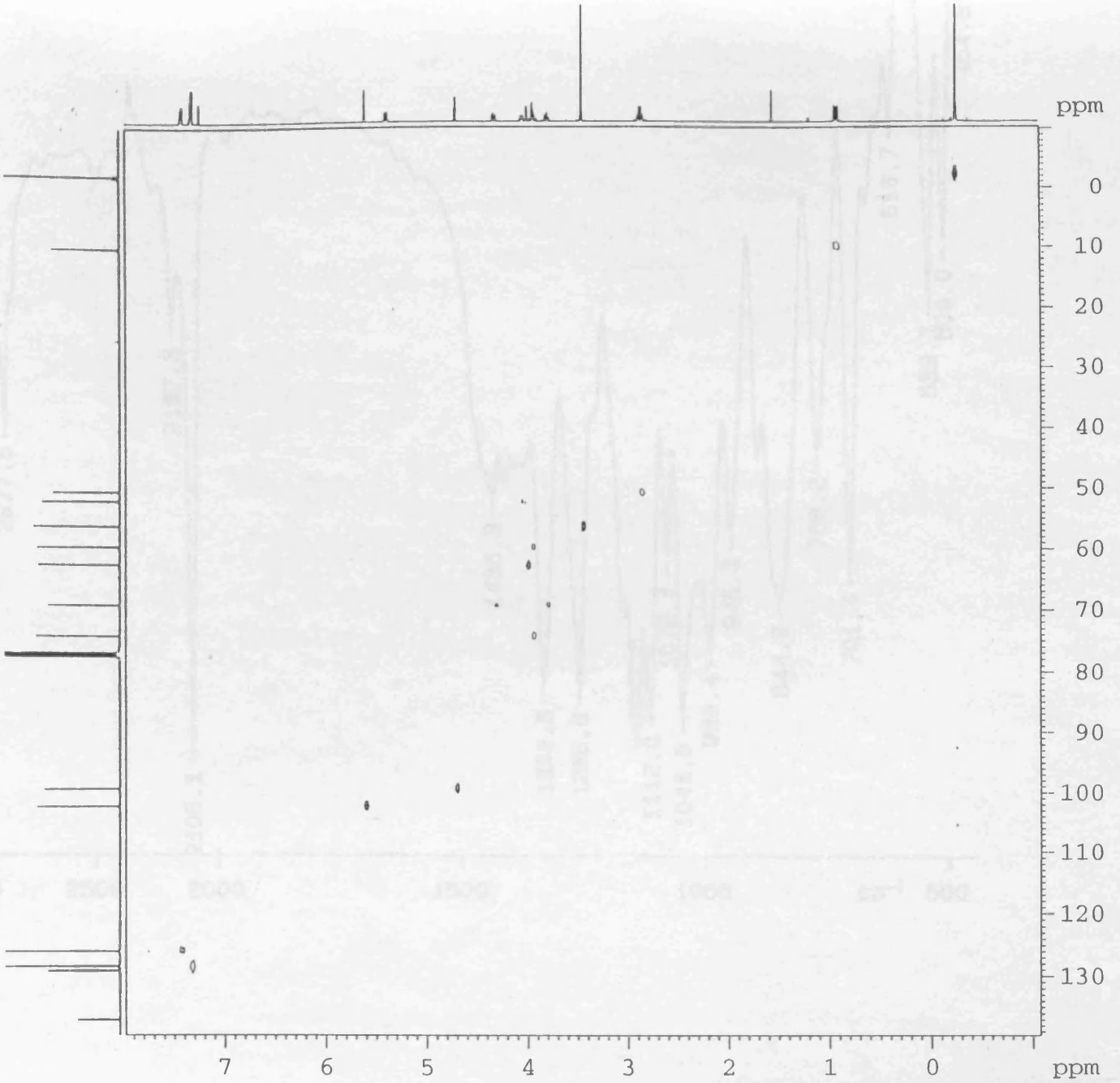
I-md-100
CDCl3, 298 K
COSY

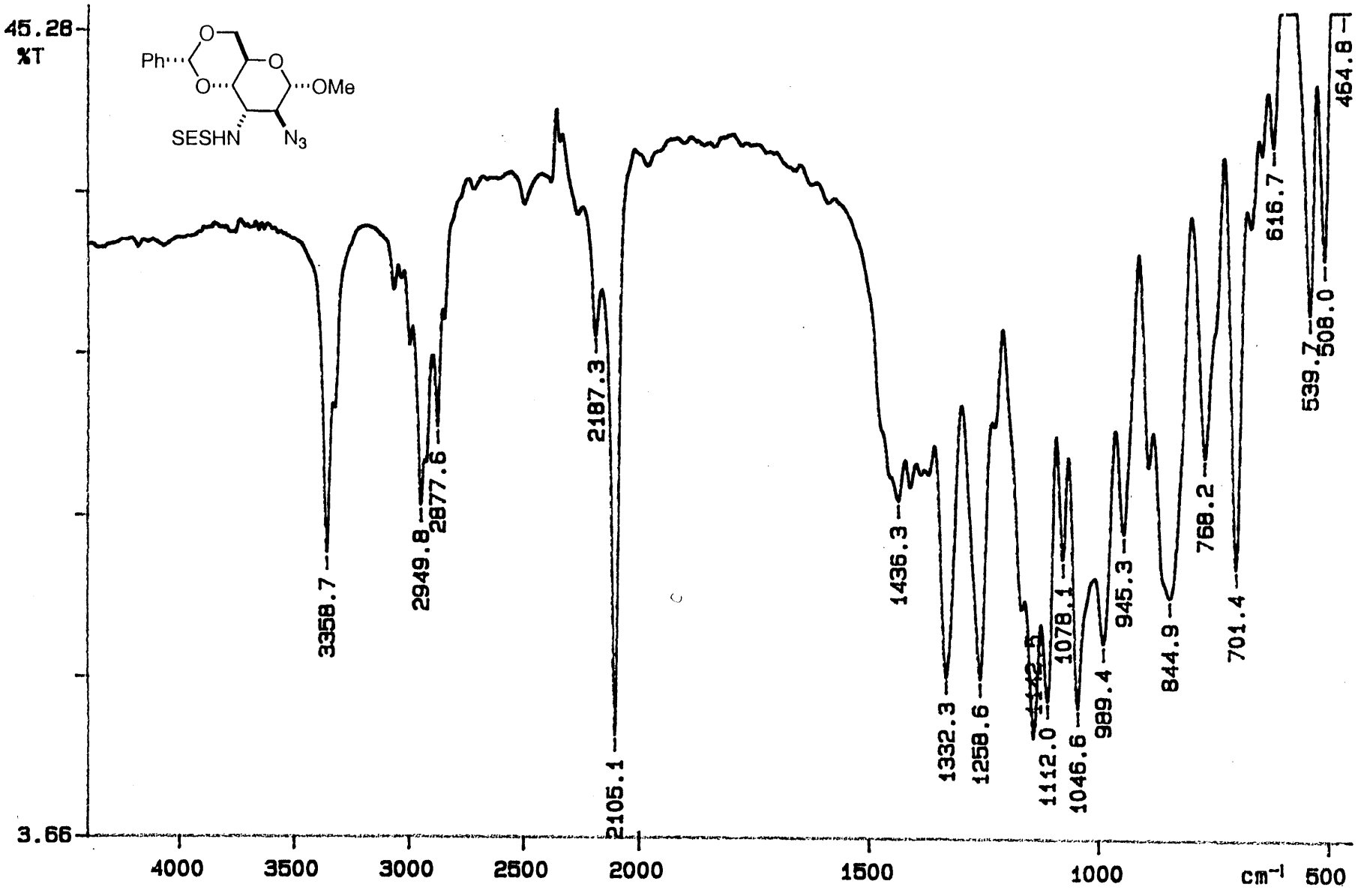




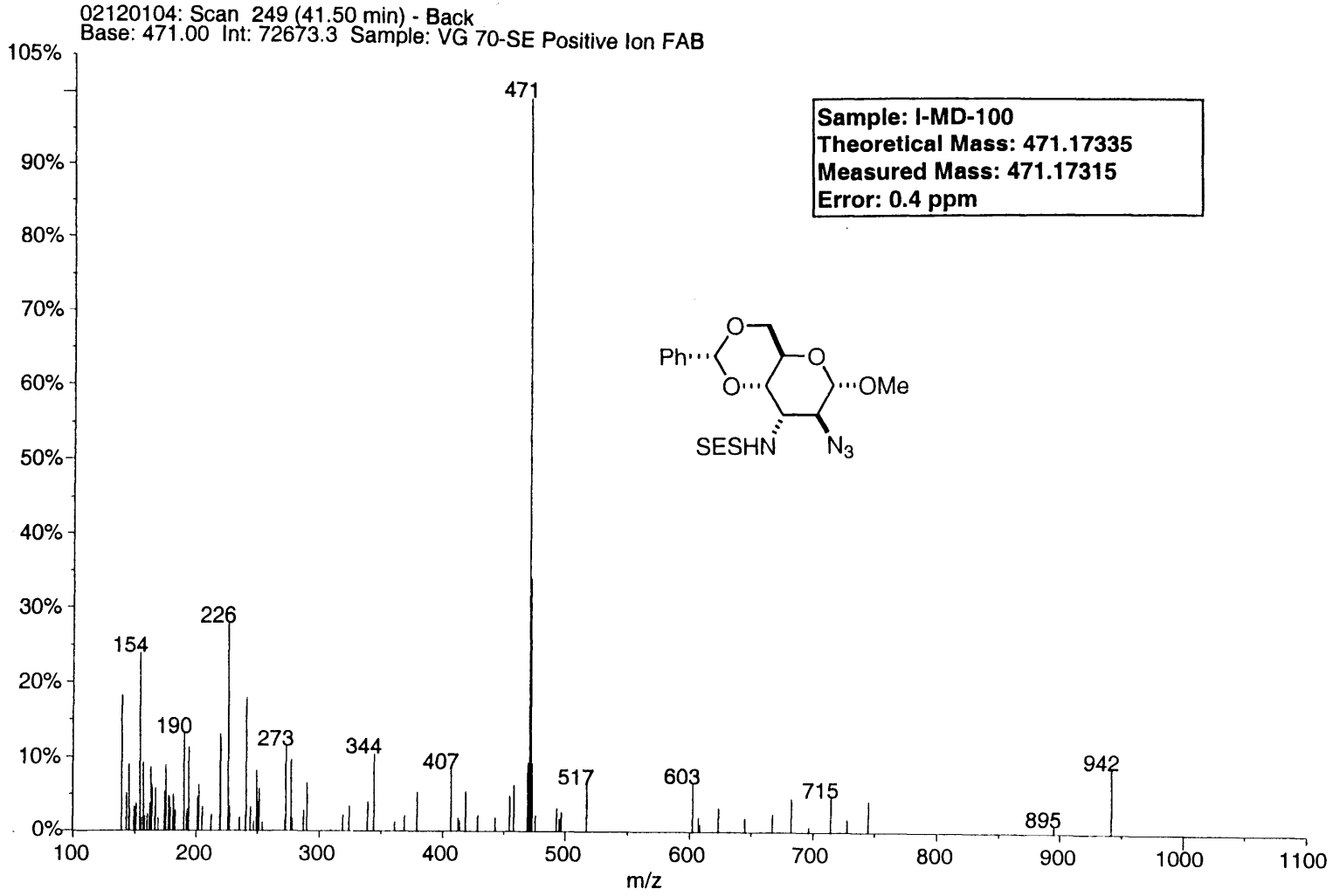
I-md-100
CDCl3, 298 K
HMQC



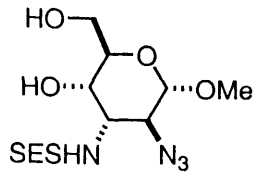




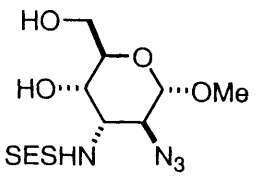
02/05/03 08:56
X: 16 scans, 16.0cm-1


02120104: Scan 249 (41.50 min) - Back
Base: 471.00 Int: 72673.3 Sample: VG 70-SE Positive Ion FAB
Sample: I-MD-100
Theoretical Mass: 471.17335
Measured Mass: 471.17315
Error: 0.4 ppm
Ph
OMe
SESHN
N3
105%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
471
226
154
190
273
344
407
517
603
715
895
942
100
200
300
400
500
600
700
800
900
1000
1100
m/z

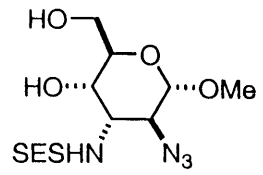
I-md-145
CDCl3, 298 K



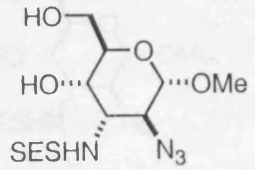
I-md-145
CDCl3, 298 K

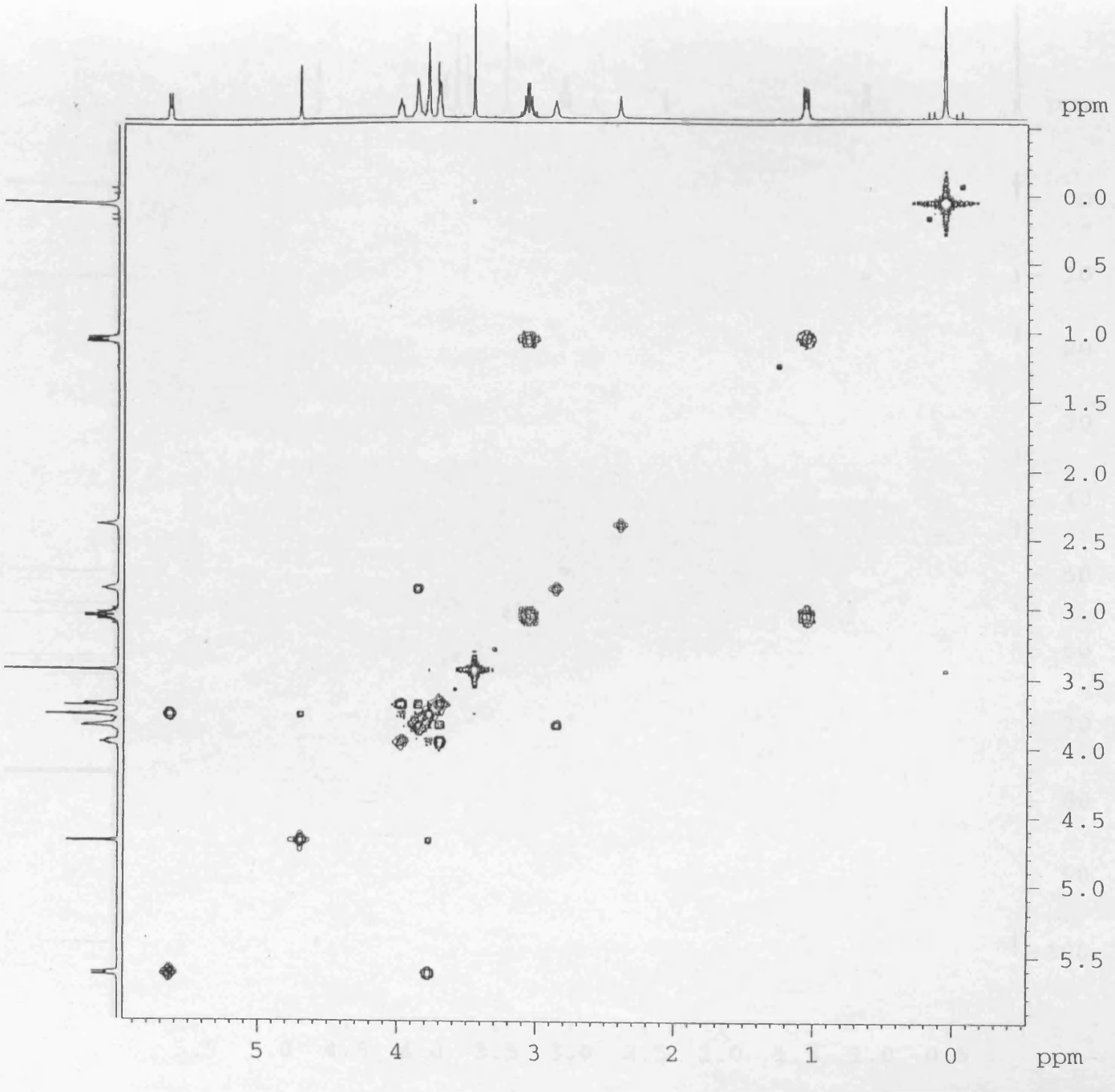


I-md-145
CDCl3, 298 K
DEPT

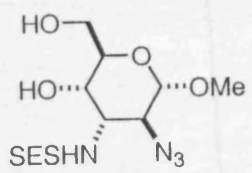


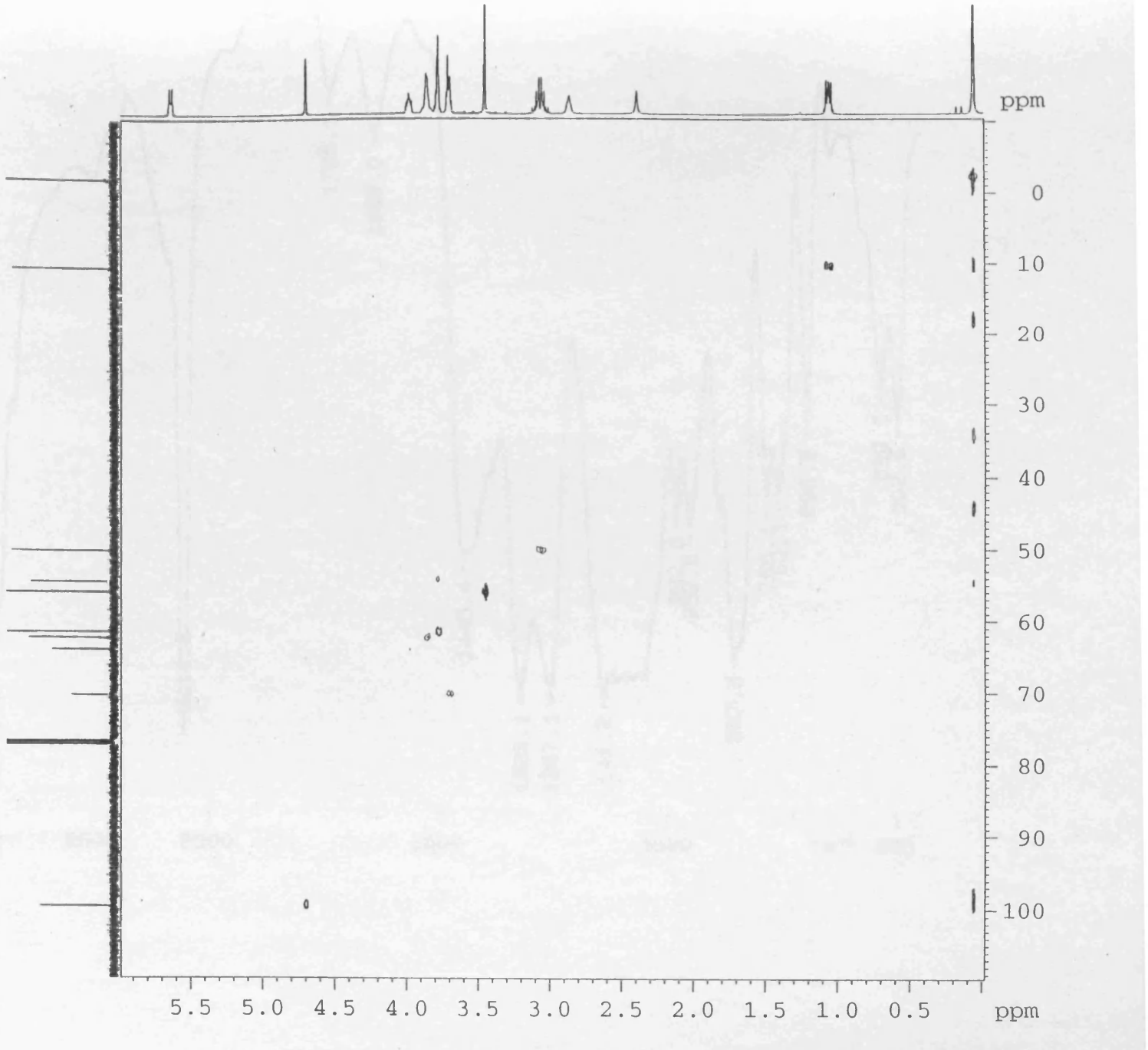
I-md-145
CDCl3, 298 K
COSY

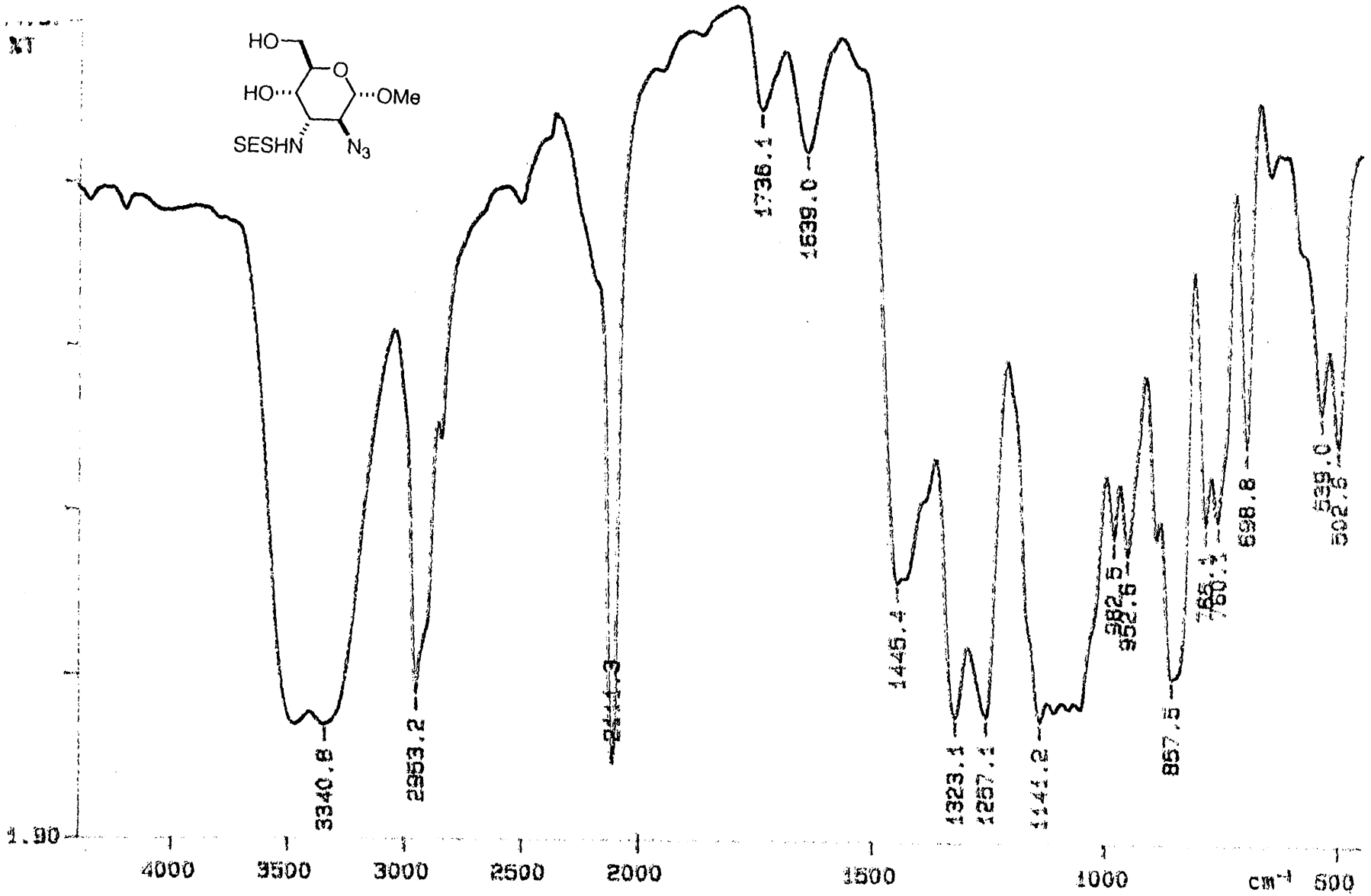




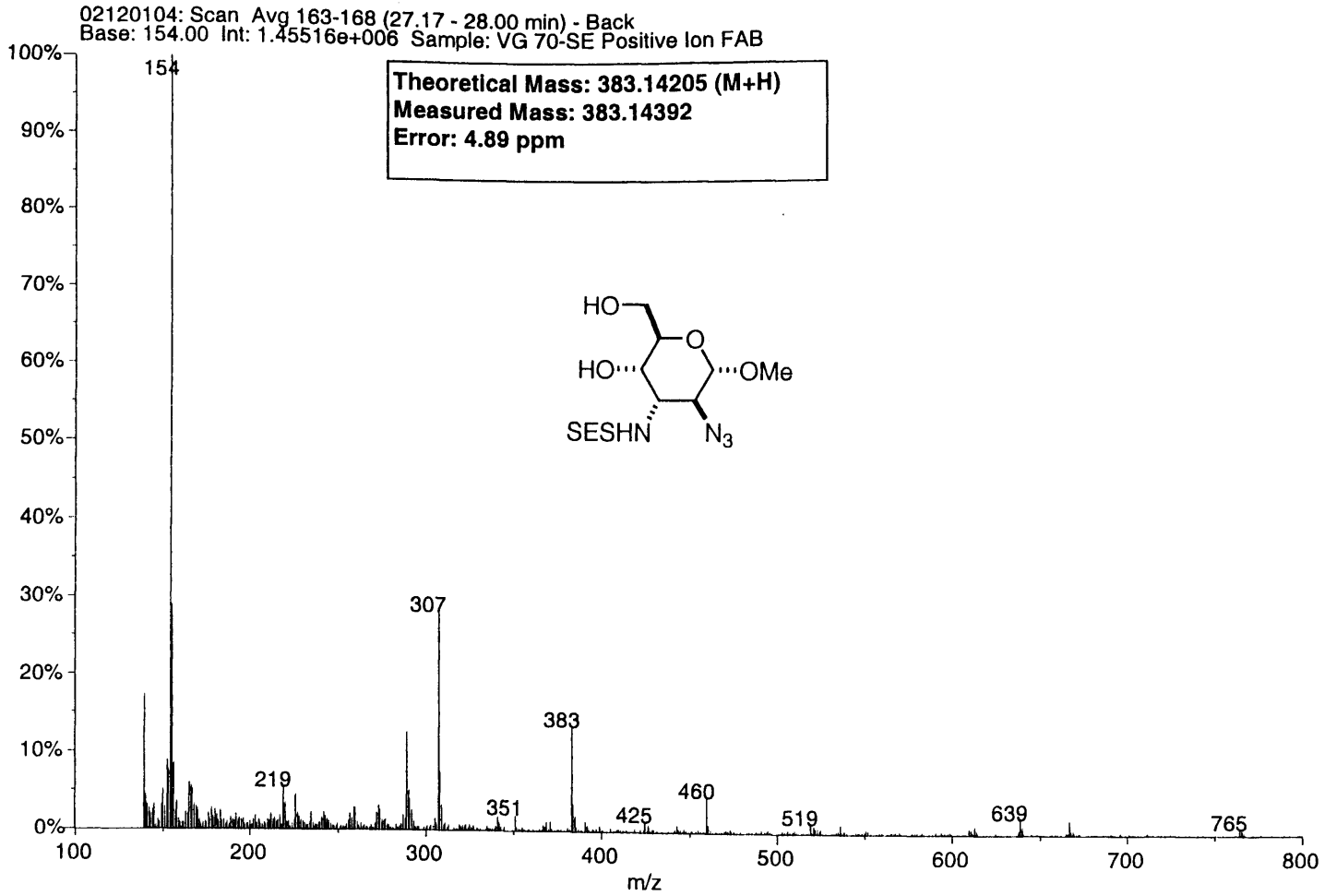
I-md-145
CDCl3, 298 K
HMQC





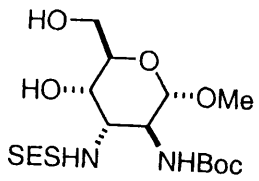


02/05/08 14:54
X: 16 scans, 16.0cm-1, flat

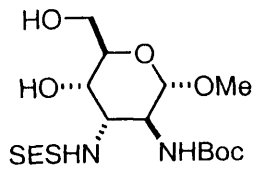

02120104: Scan Avg 163-168 (27.17 - 28.00 min) - Back
Base: 154.00 Int: 1.45516e+006 Sample: VG 70-SE Positive Ion FAB
Theoretical Mass: 383.14205 (M+H)
Measured Mass: 383.14392
Error: 4.89 ppm
HO
O
HO
OMe
SESHN
N3
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
154
307
383
219
351
425
460
519
639
765
100
200
300
400
500
600
700
800
m/z

Hi,

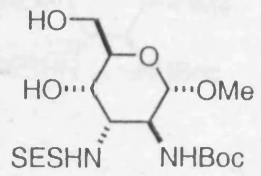
I-md-114
CDCl3, 298 K

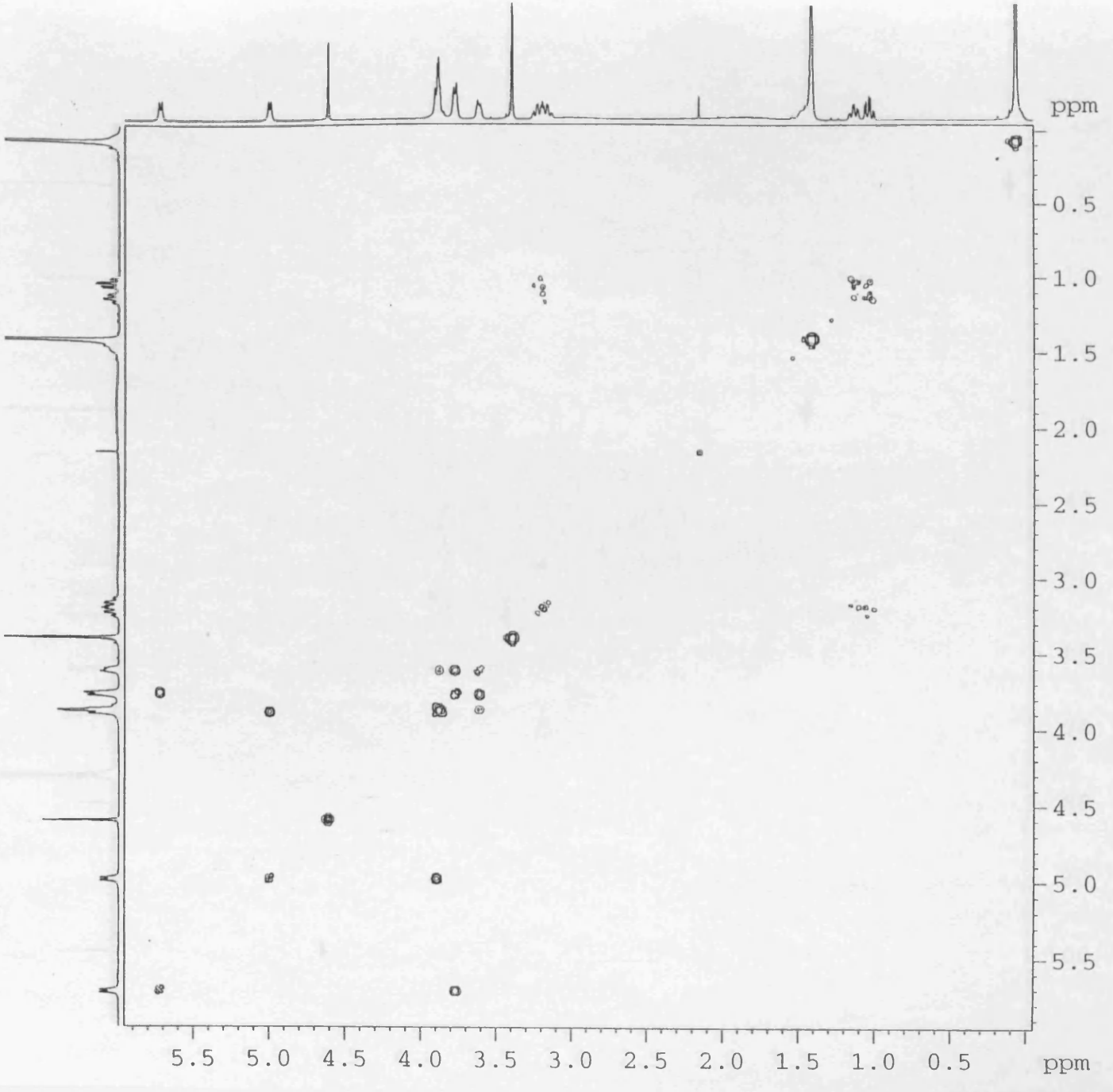


I-md-114
CDCl3, 298 K

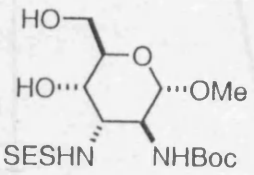


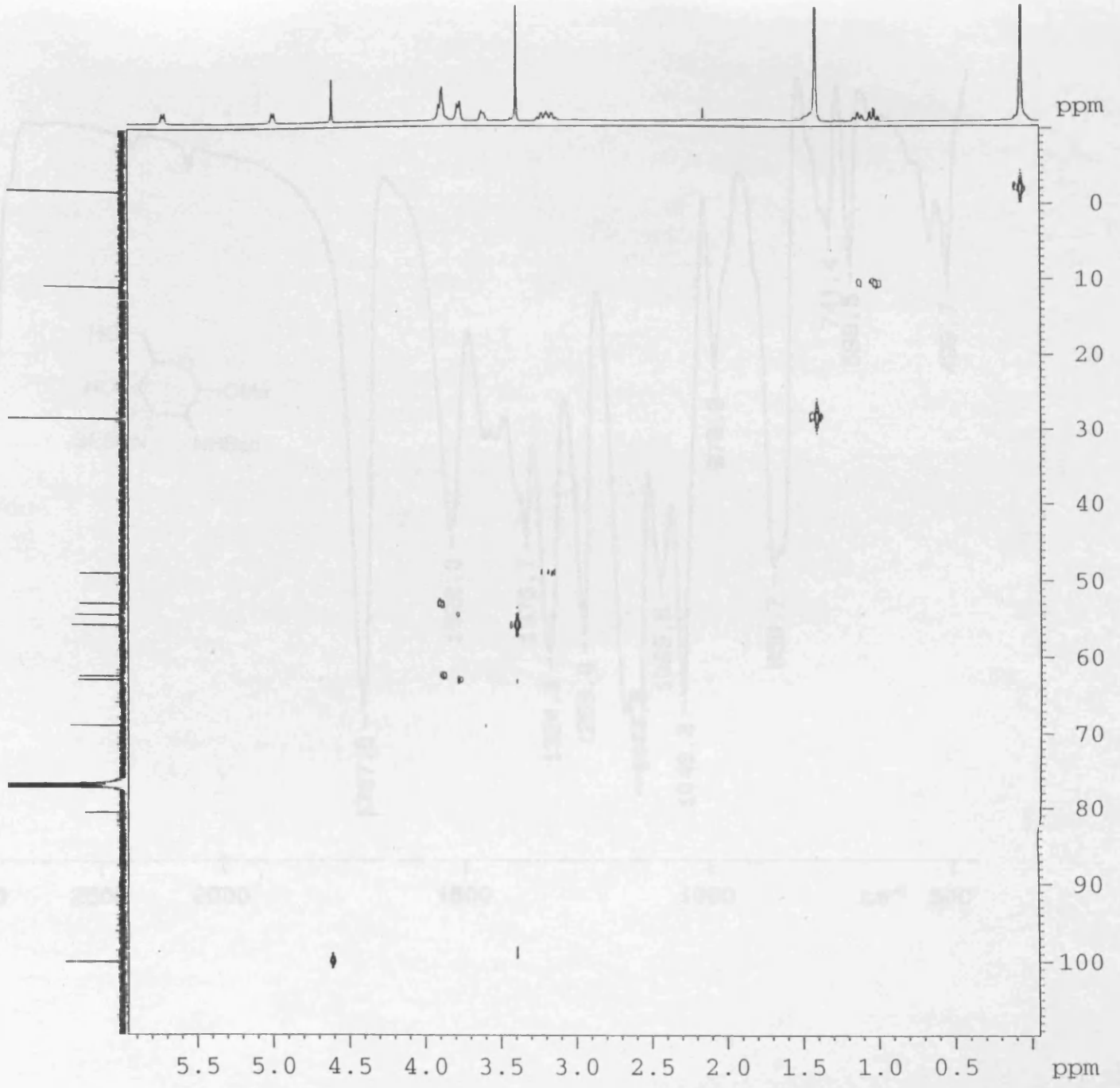
I-md-114
CDCl3, 298 K
COSY



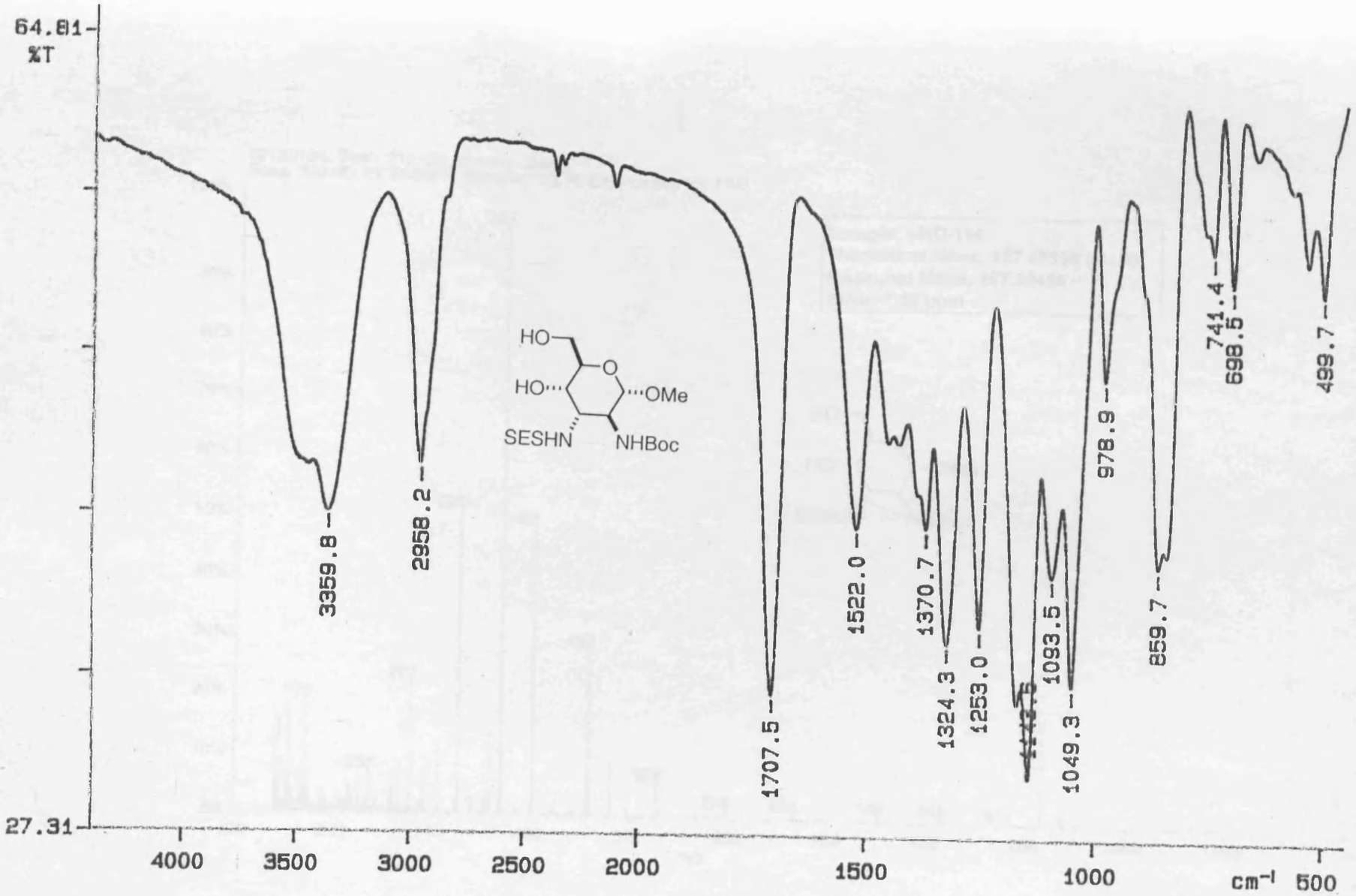


I-md-114
CDCl3, 298 K
HMQC

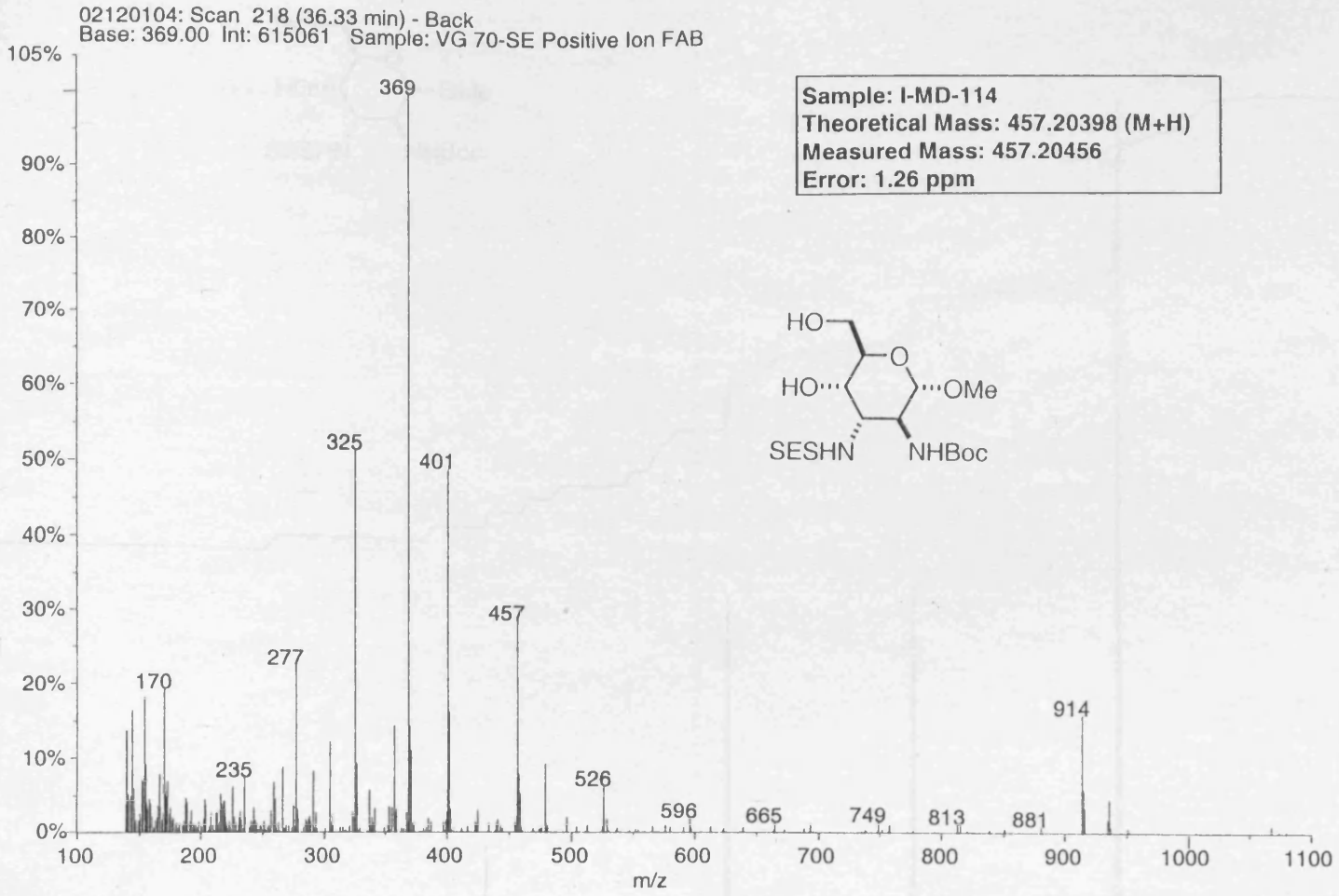




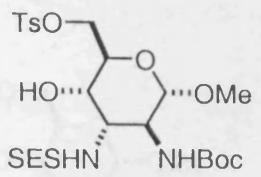
PERKIN ELMER



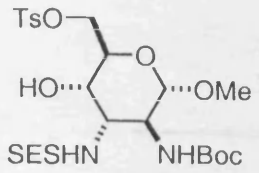
02/05/03 14:18
X: 16 scans, 16.0cm-1, flat


02120104: Scan 218 (36.33 min) - Back
Base: 369.00 Int: 615061 Sample: VG 70-SE Positive Ion FAB
Sample: I-MD-114
Theoretical Mass: 457.20398 (M+H)
Measured Mass: 457.20456
Error: 1.26 ppm
HO
O
HO
OMe
SESHN
NHBoc
105%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
369
325
401
457
277
170
235
526
596
665
749
813
881
914
100
200
300
400
500
600
700
800
900
1000
1100
m/z

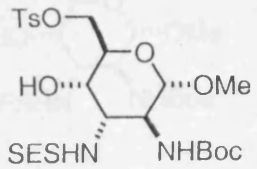
I-md-122
CDCl3, 298 K

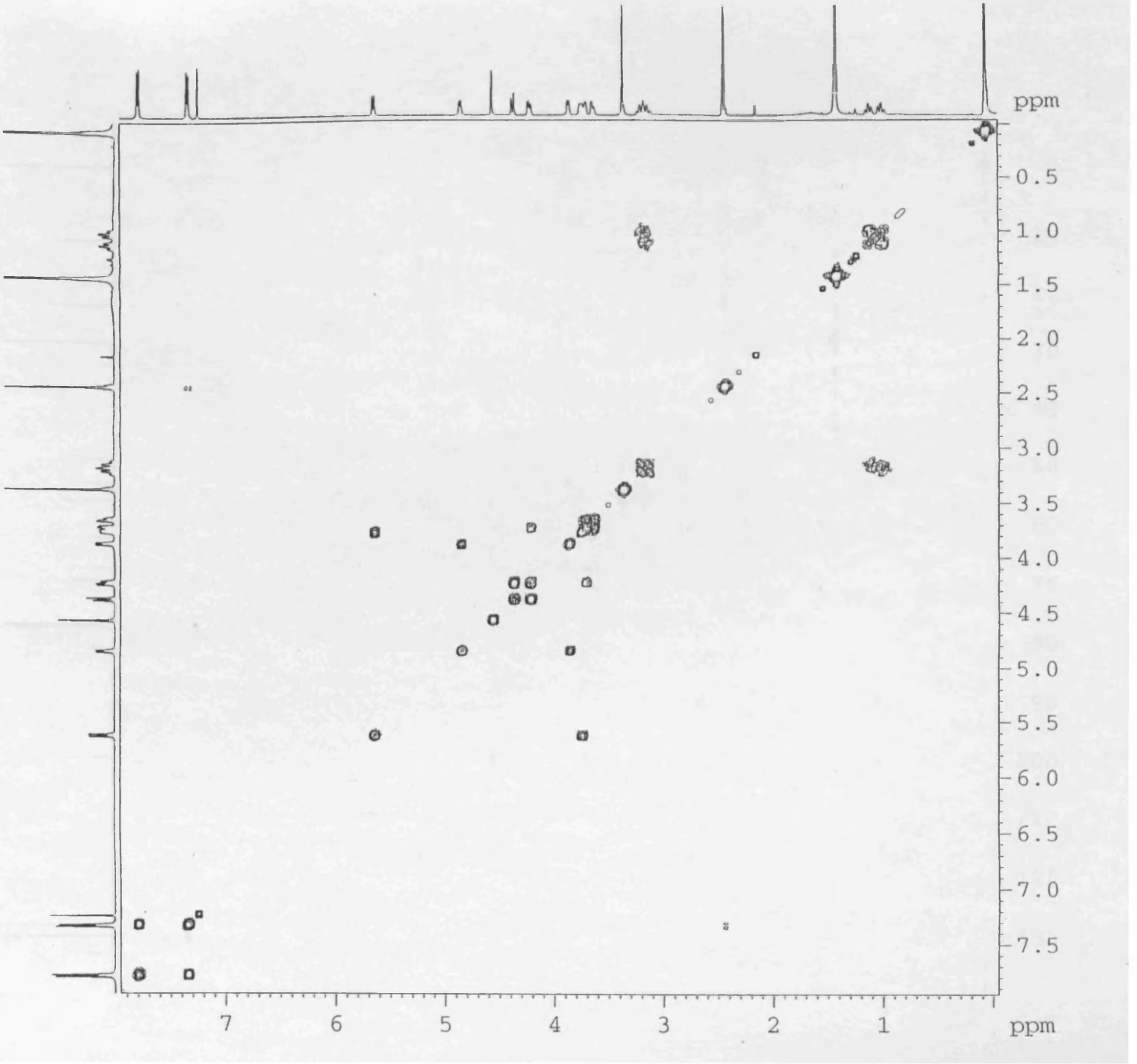


I-md-122
CDCl3, 298 K

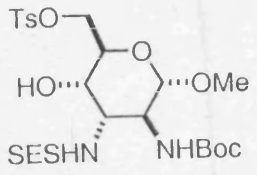


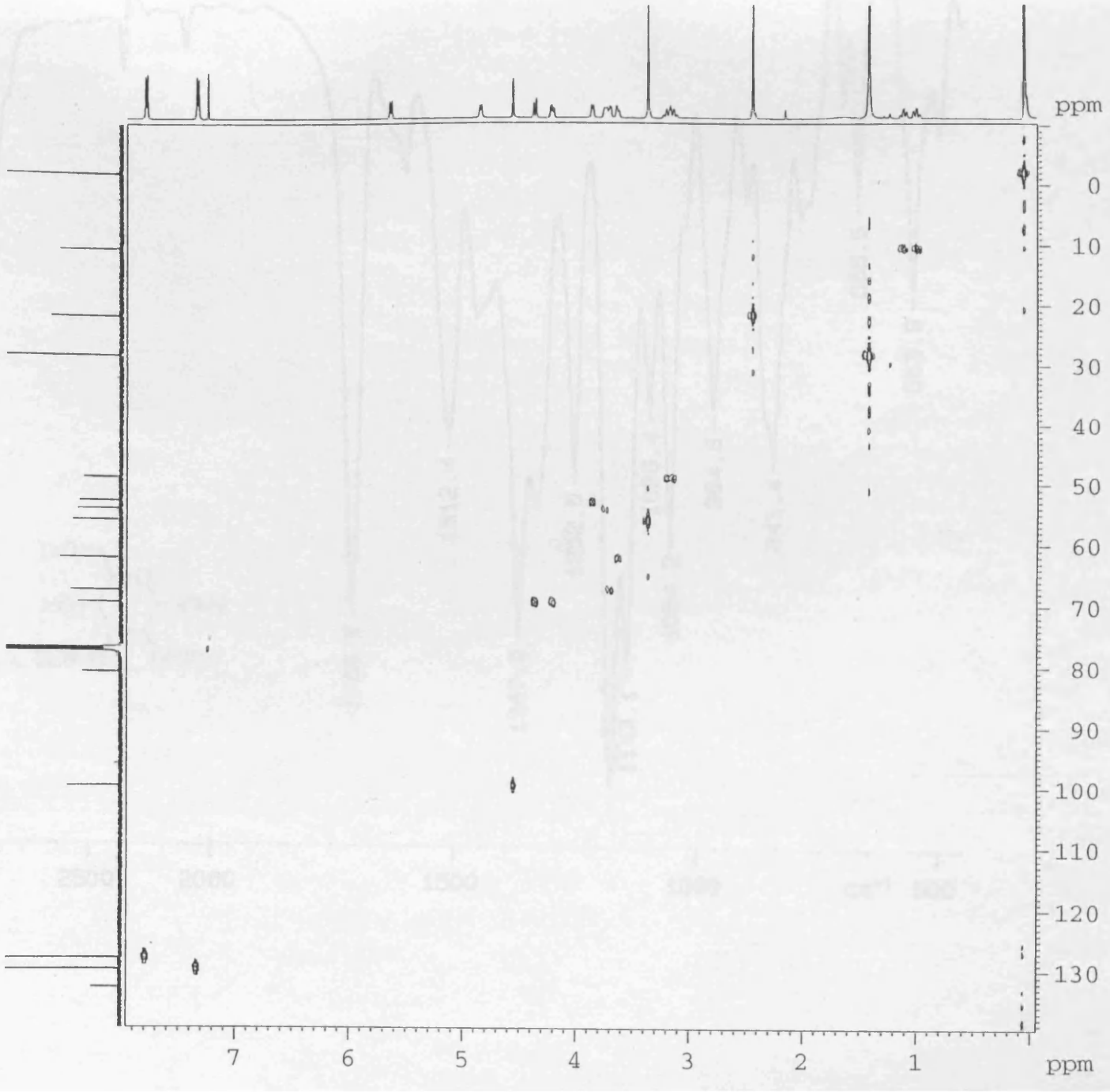
I-md-122
CDCl3, 298 K
COSY

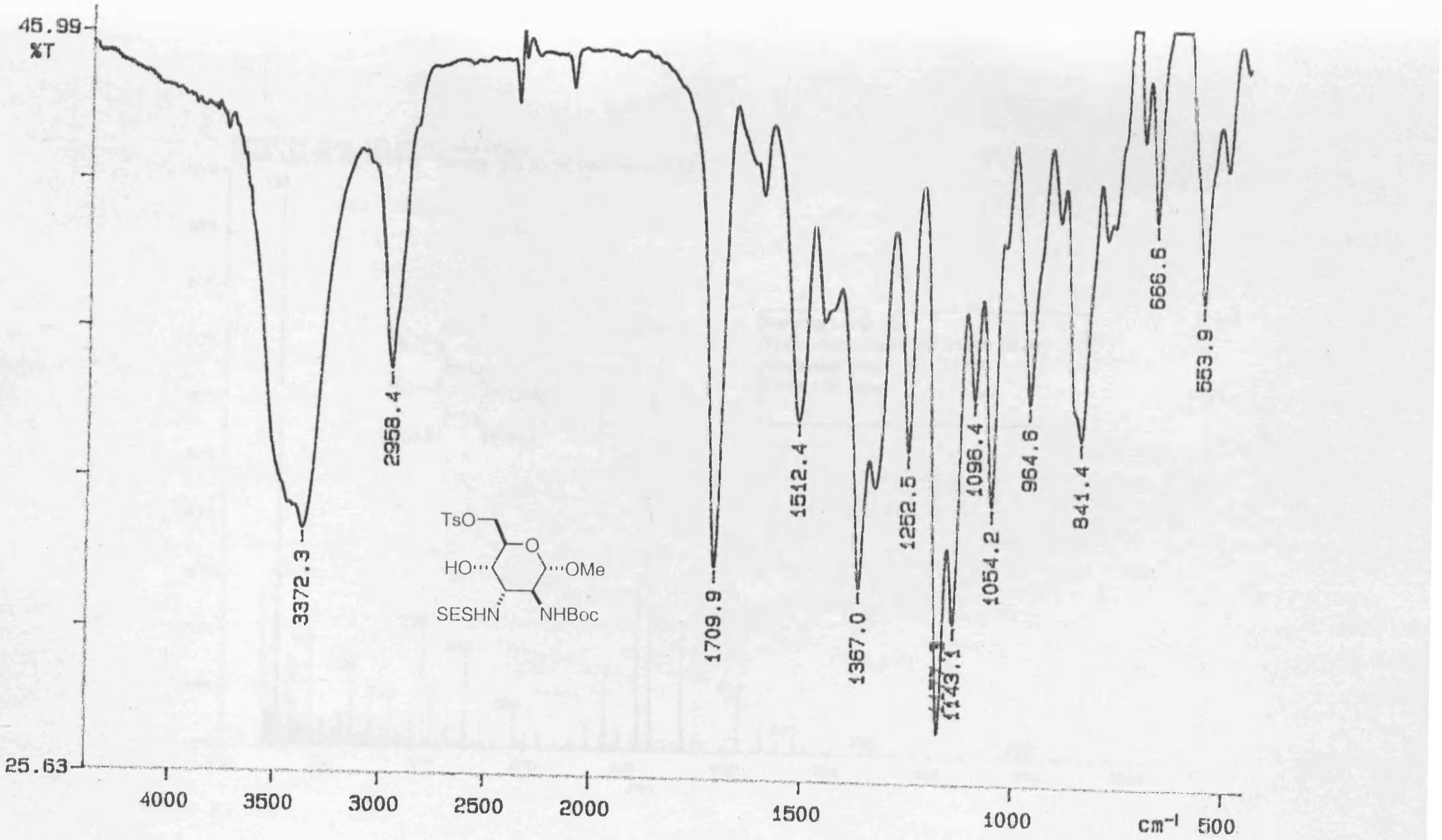




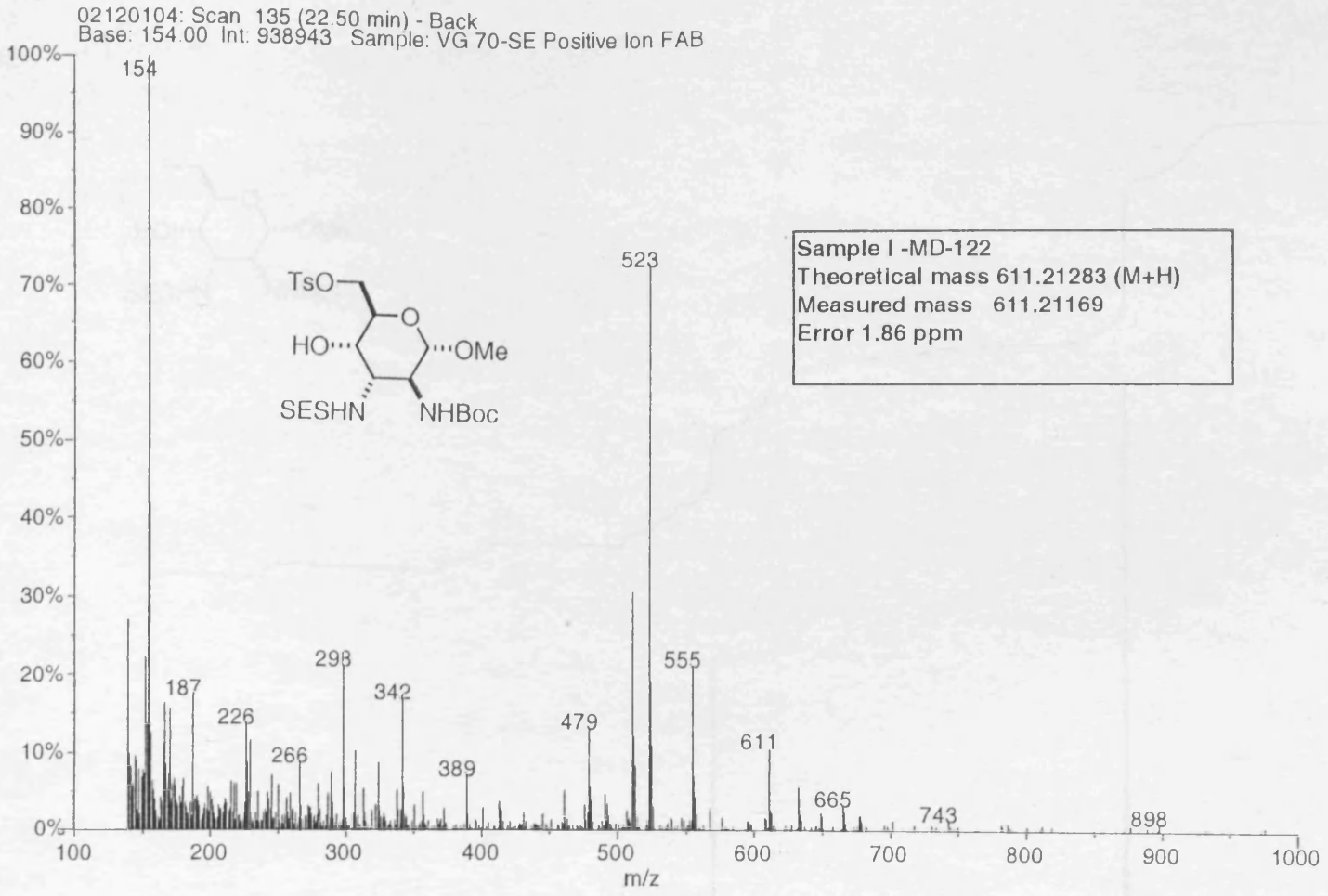
I-md-122
CDCl3, 298 K
HMQC



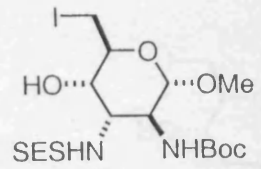




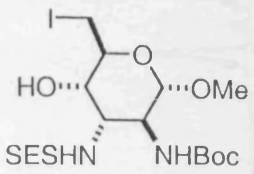
02/05/08 14:31
X: 16 scans, 16.0cm-1, flat


02120104: Scan 135 (22.50 min) - Back
Base: 154.00 Int: 938943 Sample: VG 70-SE Positive Ion FAB
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
154
523
555
298
342
187
226
266
389
479
611
665
743
898
100
200
300
400
500
600
700
800
900
1000
m/z
TsO
O
HO
OMe
SESHN
NHBoc
Sample I -MD-122
Theoretical mass 611.21283 (M+H)
Measured mass 611.21169
Error 1.86 ppm

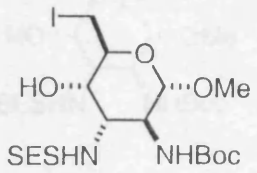
I-md-125
CDC13, 298 K

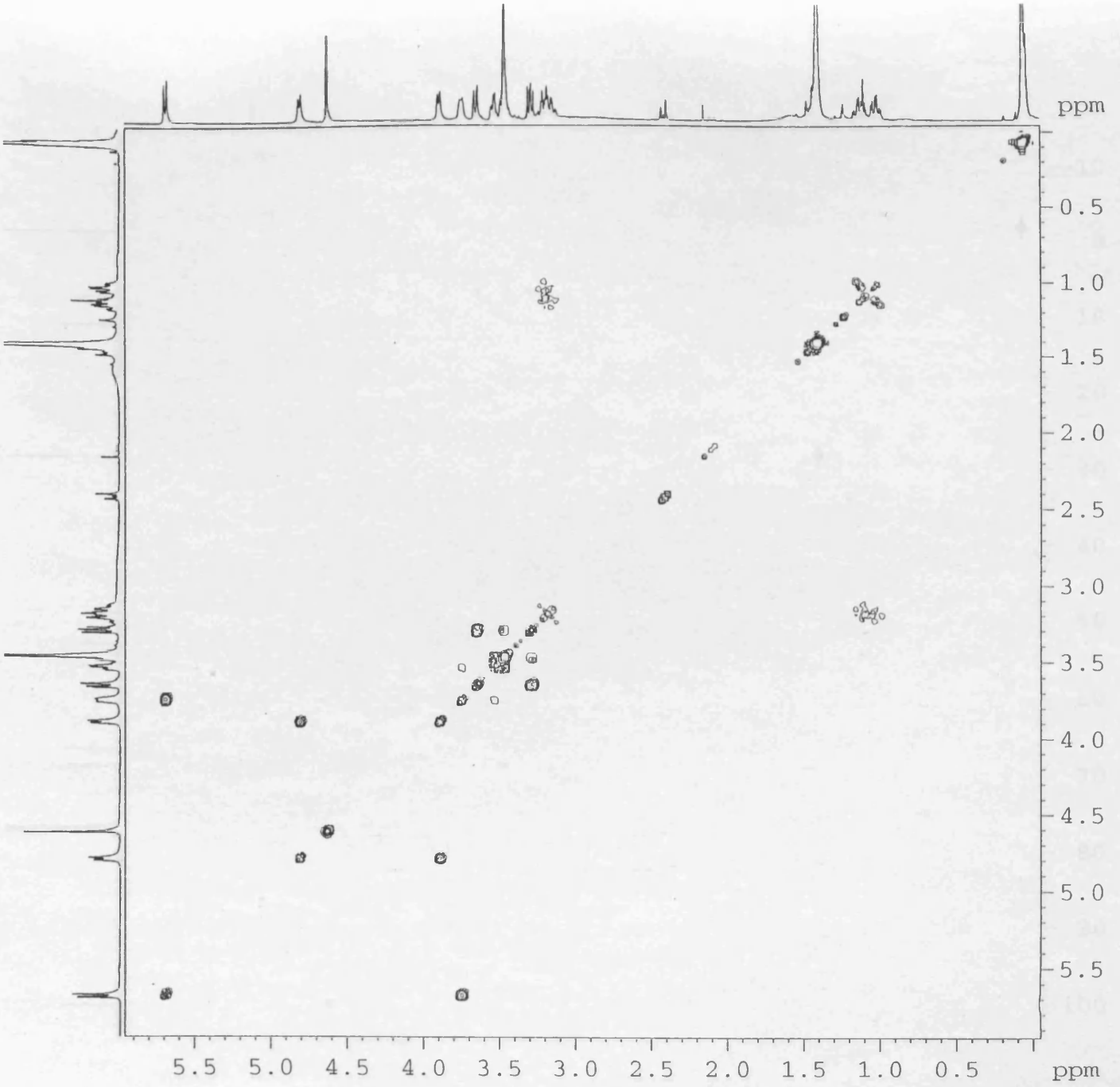


I-md-125
CDCl3, 298 K

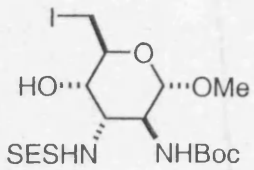


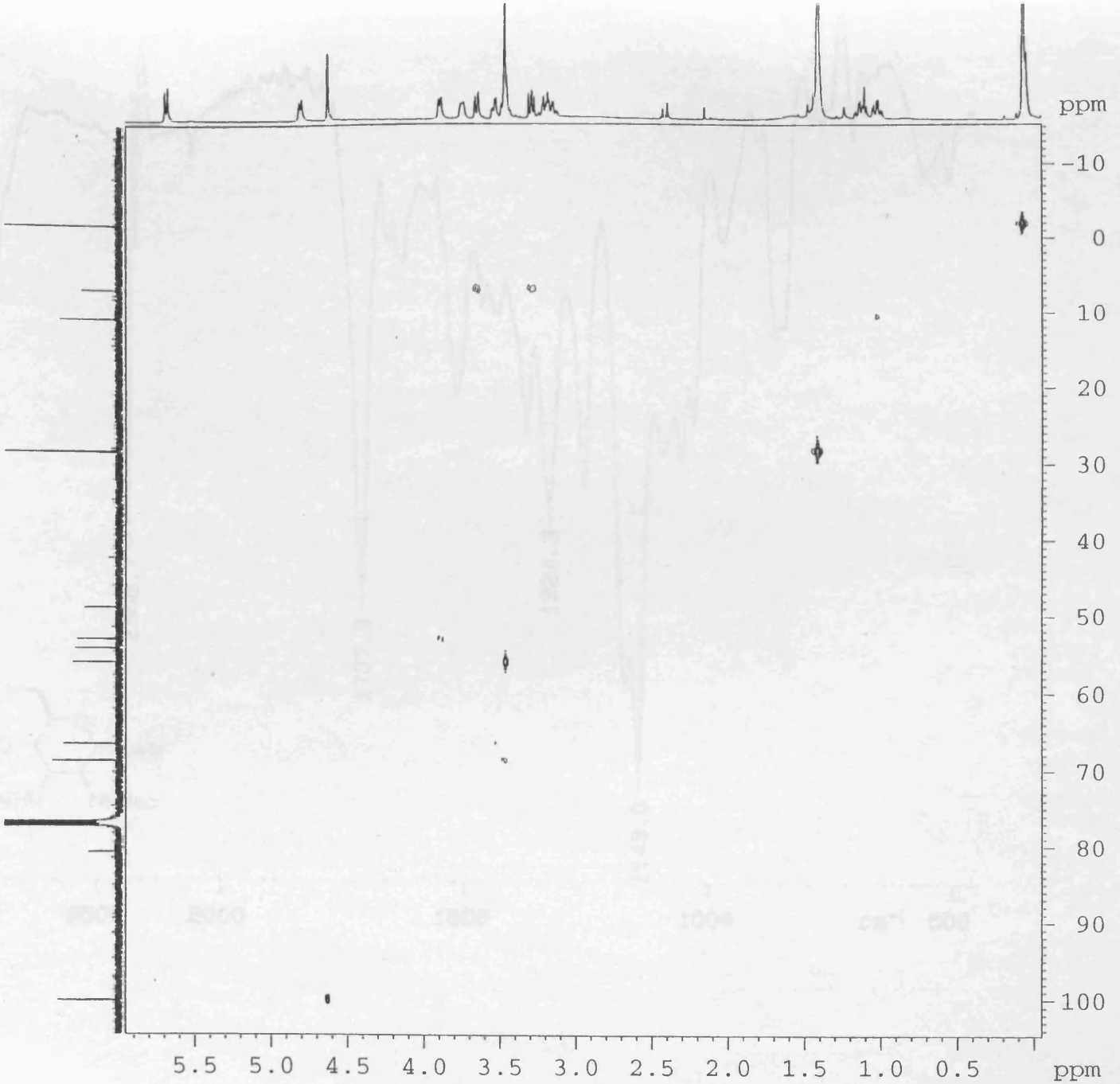
I-md-125
CDCl3, 298 K
COSY

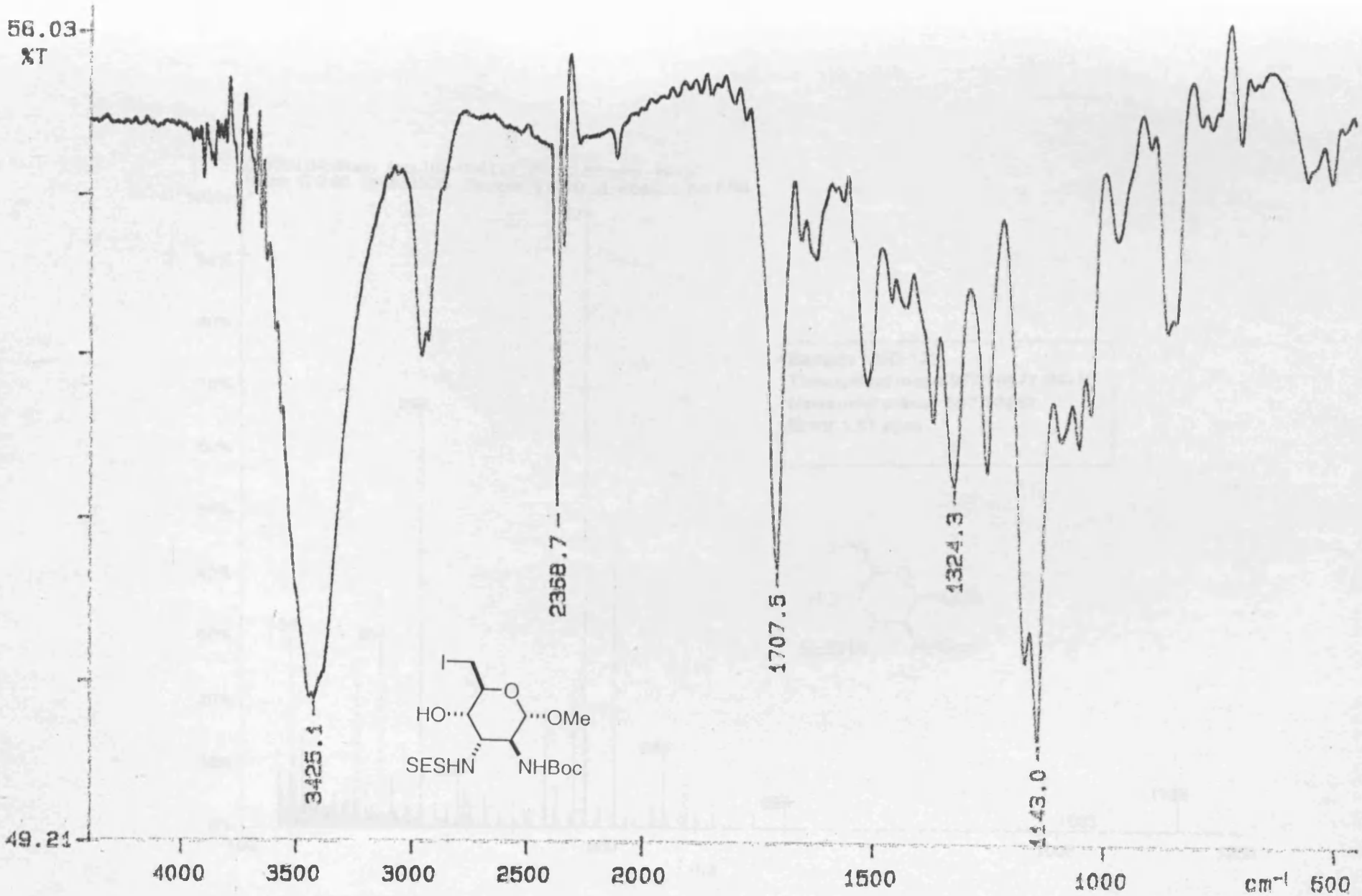




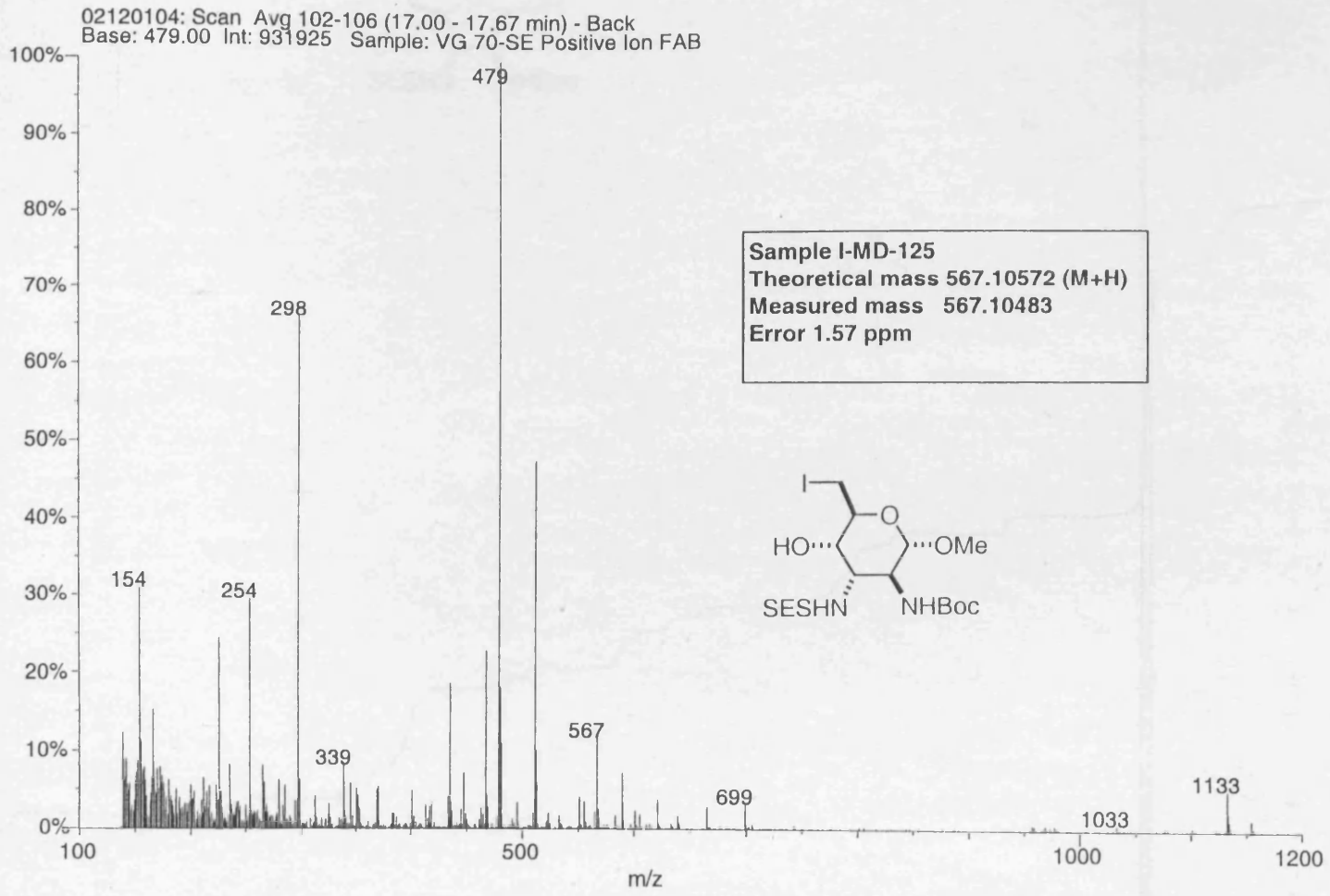
I-md-125
CDCl3, 298 K
HMQC



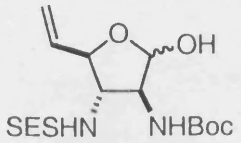




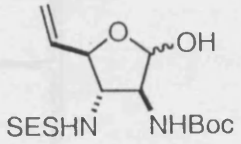
02/05/08 14:44
X: 16 scans, 16.0cm-1, flat


02120104: Scan Avg 102-106 (17.00 - 17.67 min) - Back
Base: 479.00 Int: 931925 Sample: VG 70-SE Positive Ion FAB
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
479
298
154
254
339
567
699
1033
1133
100
500
1000
1200
m/z
Sample I-MD-125
Theoretical mass 567.10572 (M+H)
Measured mass 567.10483
Error 1.57 ppm
I
O
HO
OMe
SESHN
NHBoc

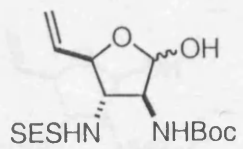
I-md-136
toluene-d8, 373 K

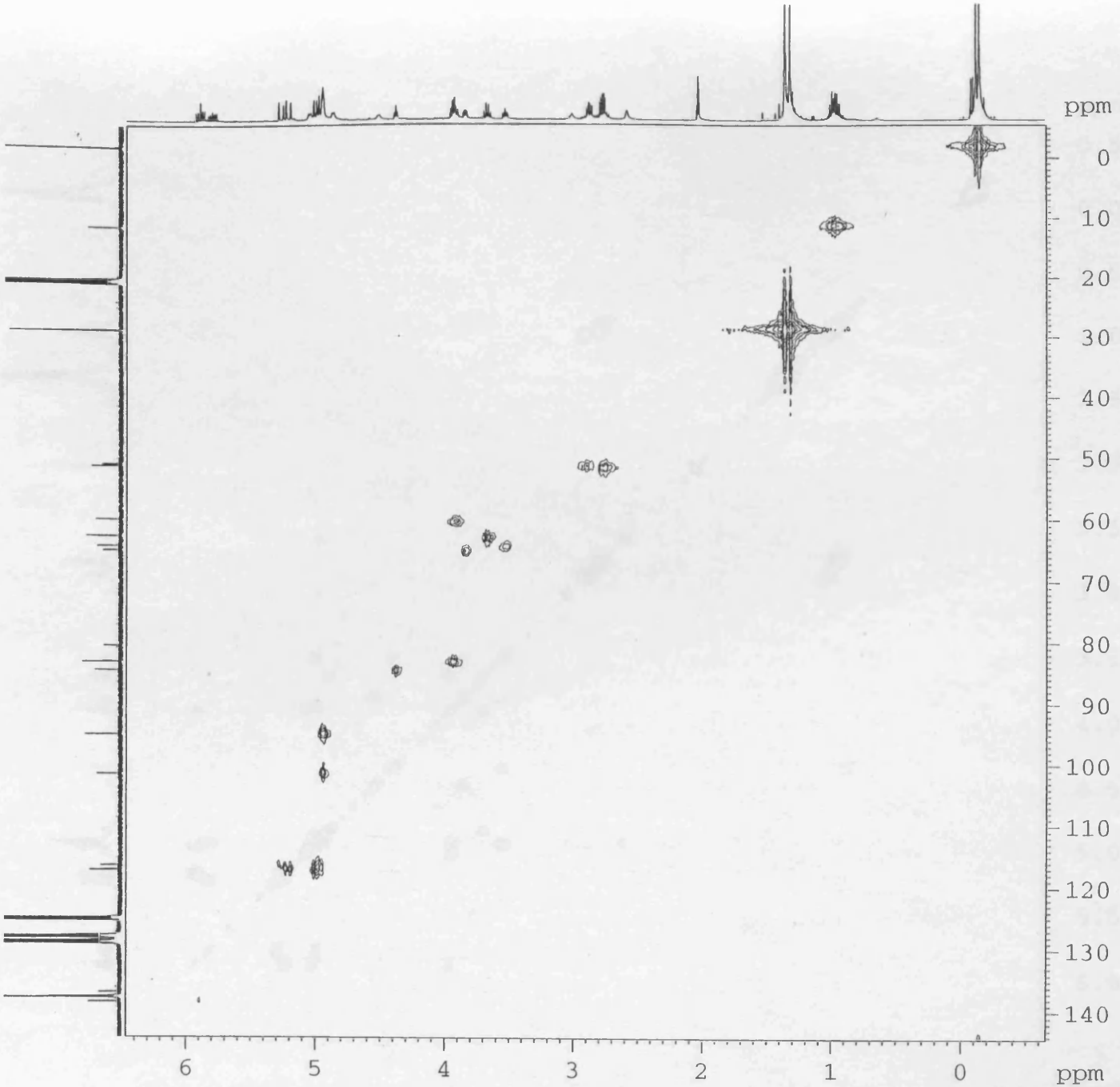


I-md-136
toluene-d8, 373 K

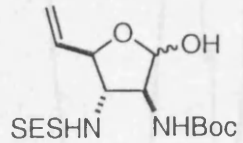


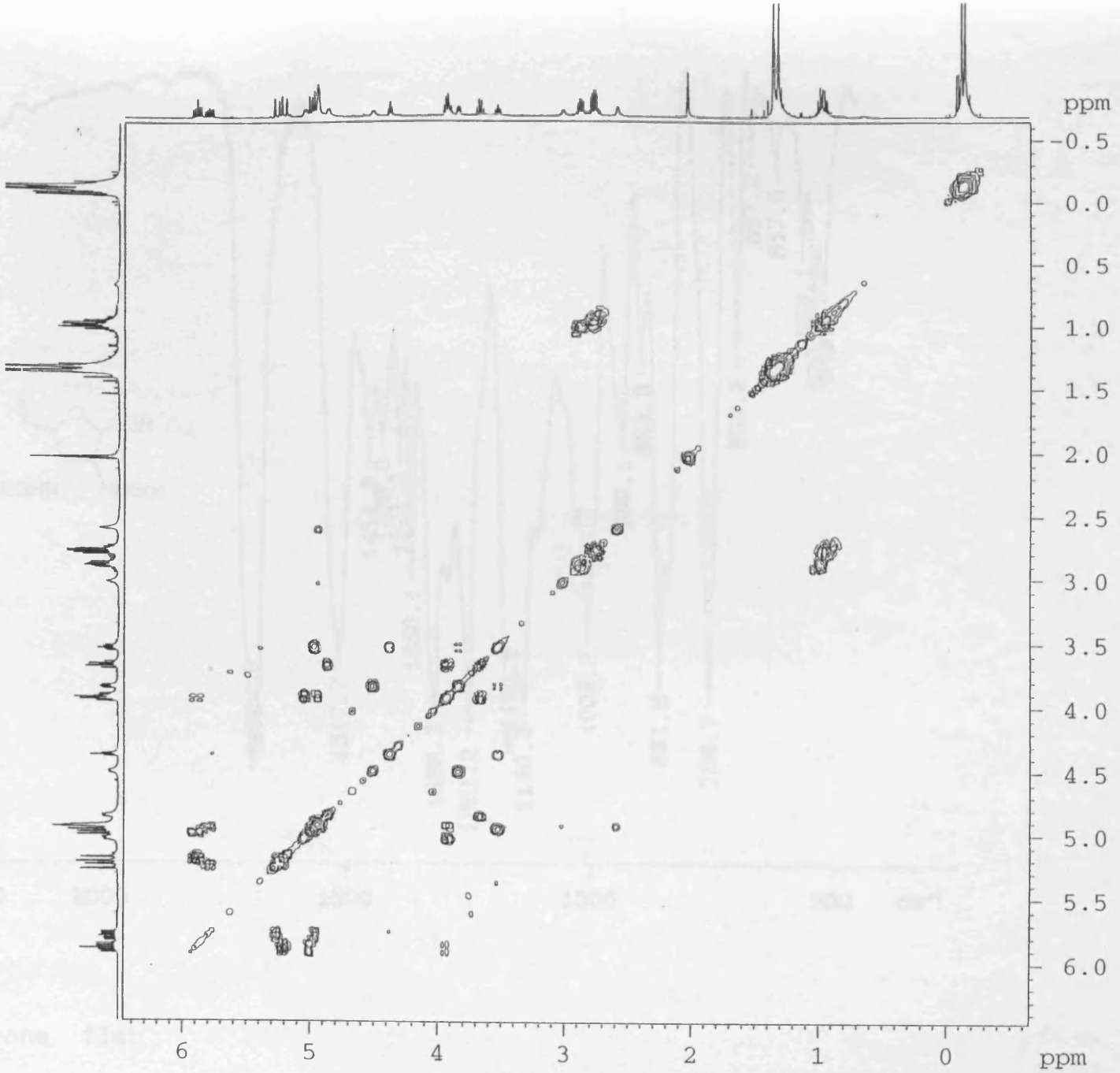
I-md-136
toluene-d8, 373 K
HMQC

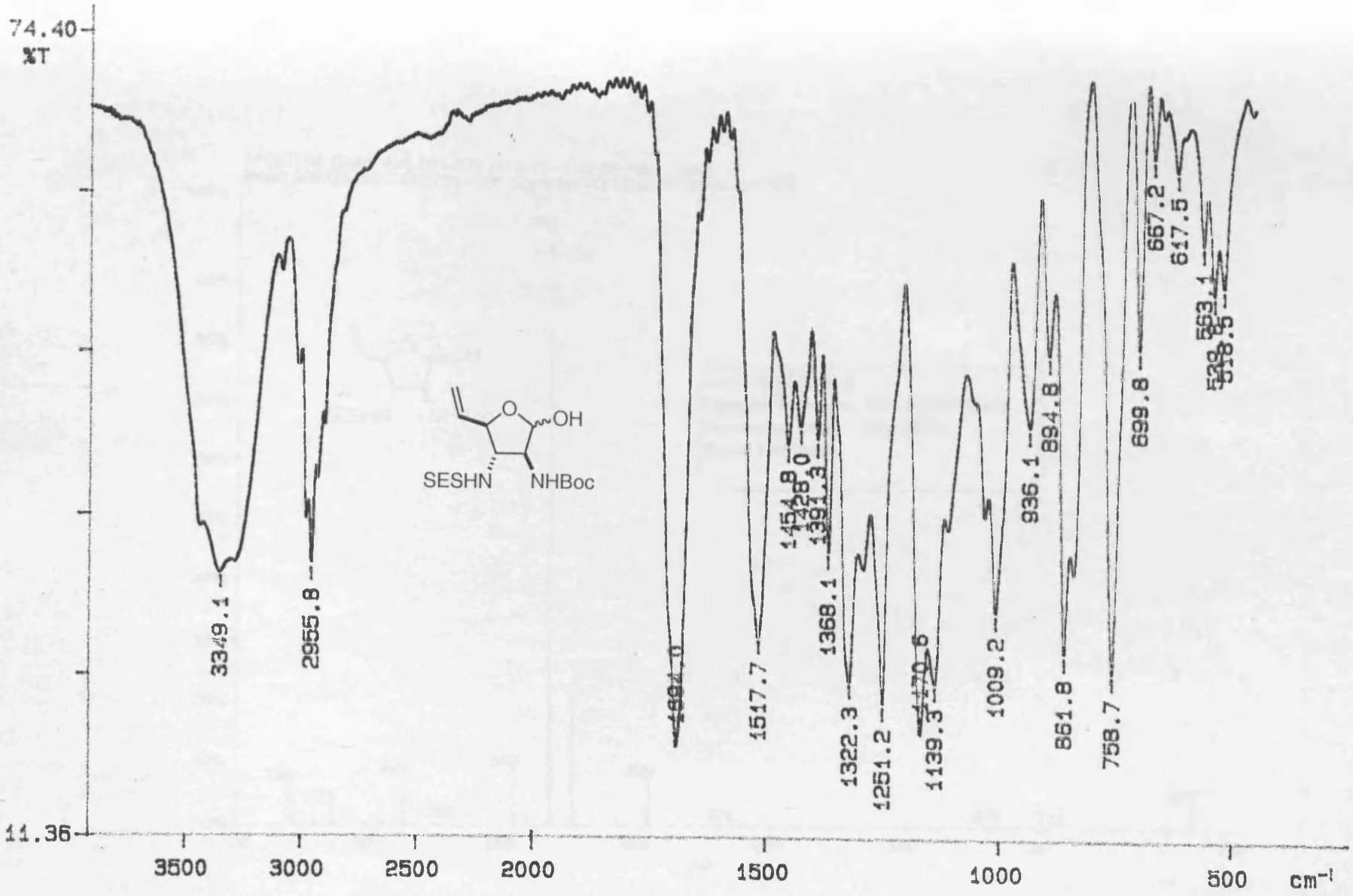




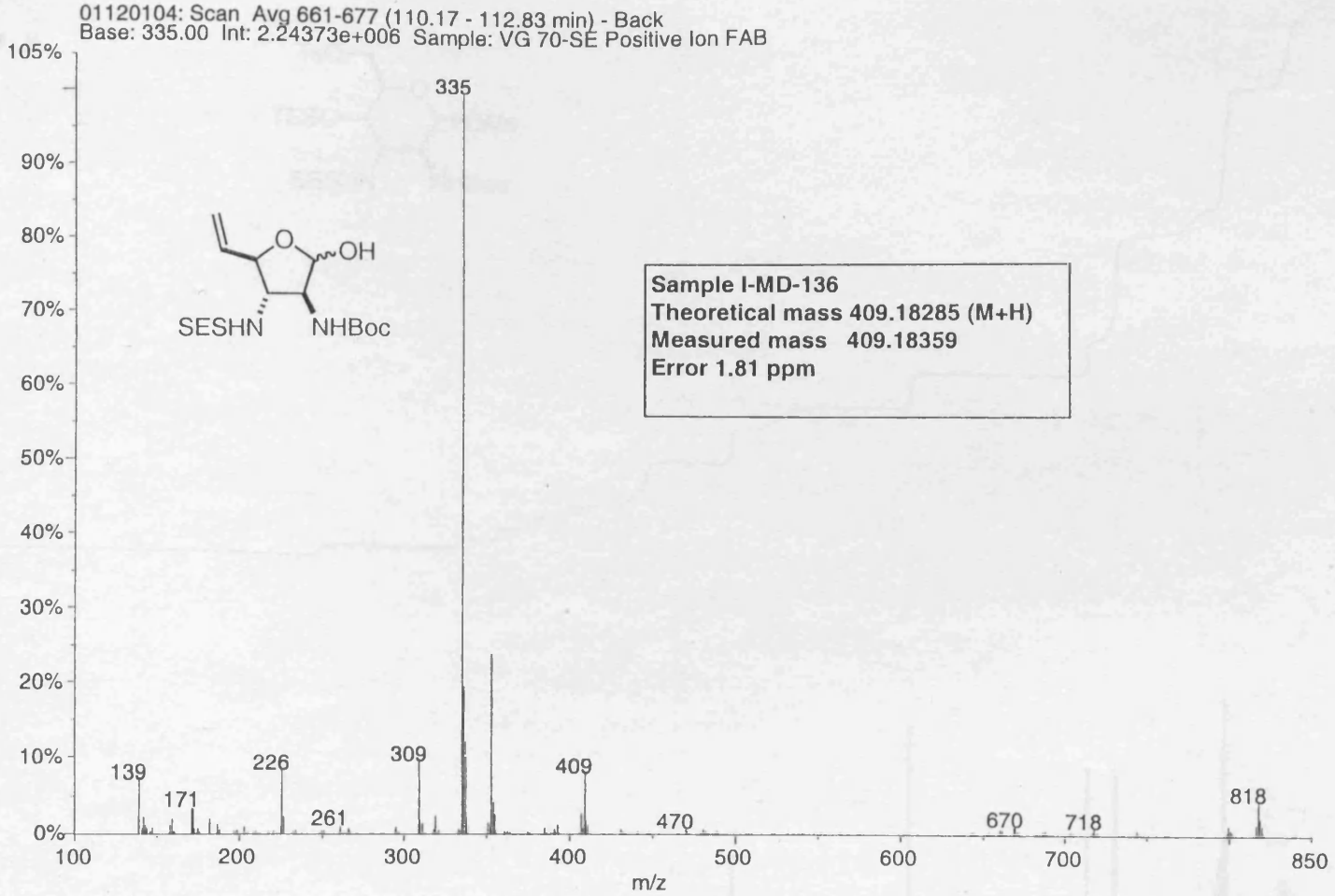
I-md-136
toluene-d8, 373 K
COSY



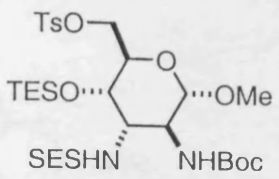




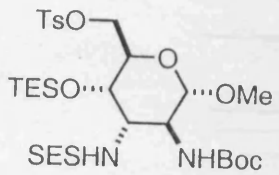
03/01/16 10:56
X: 16 scans, 16.0cm-1, apod none, flat


01120104: Scan Avg 661-677 (110.17 - 112.83 min) - Back
Base: 335.00 Int: 2.24373e+006 Sample: VG 70-SE Positive Ion FAB
105%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
335
139
171
226
261
309
409
470
670
718
818
100
200
300
400
500
600
700
850
m/z
O
OH
SESHN
NHBoc
Sample I-MD-136
Theoretical mass 409.18285 (M+H)
Measured mass 409.18359
Error 1.81 ppm

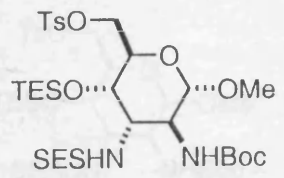
II-md-6
CDCl3, 298 K

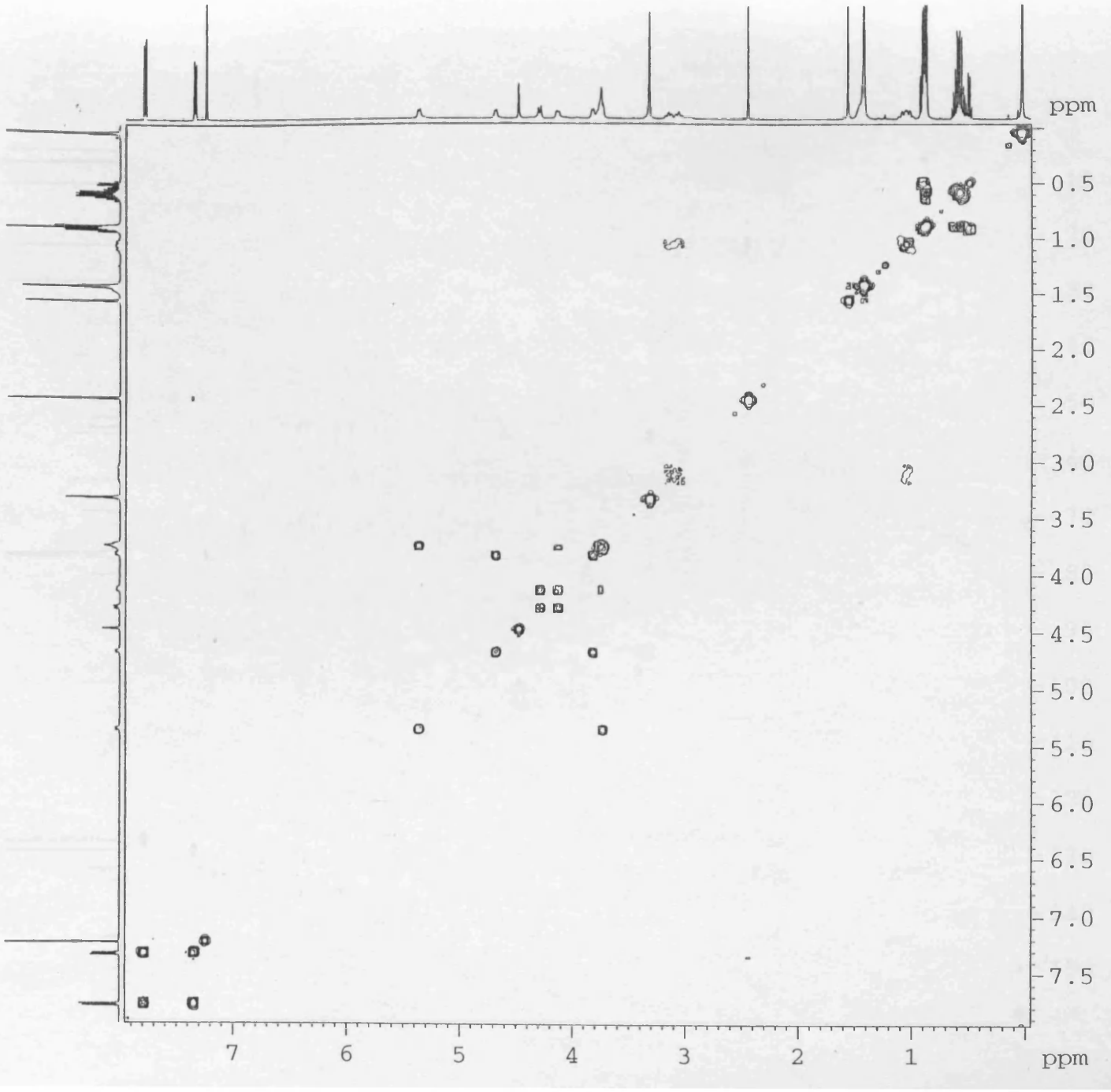


II-md-6
CDCl3, 298 K

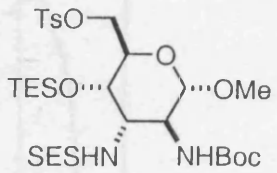


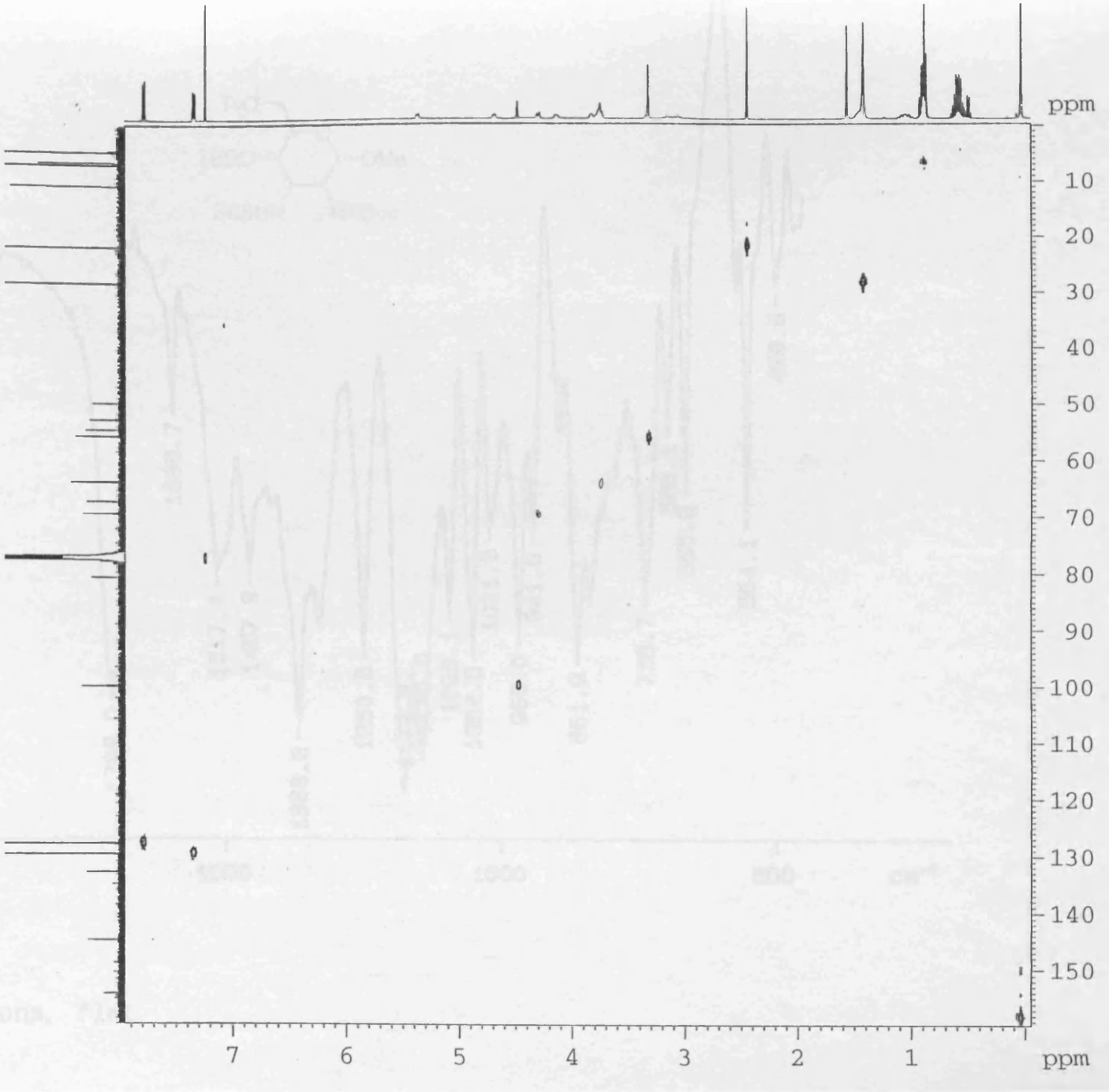
II-md-6
CDCl3, 298 K
COSY

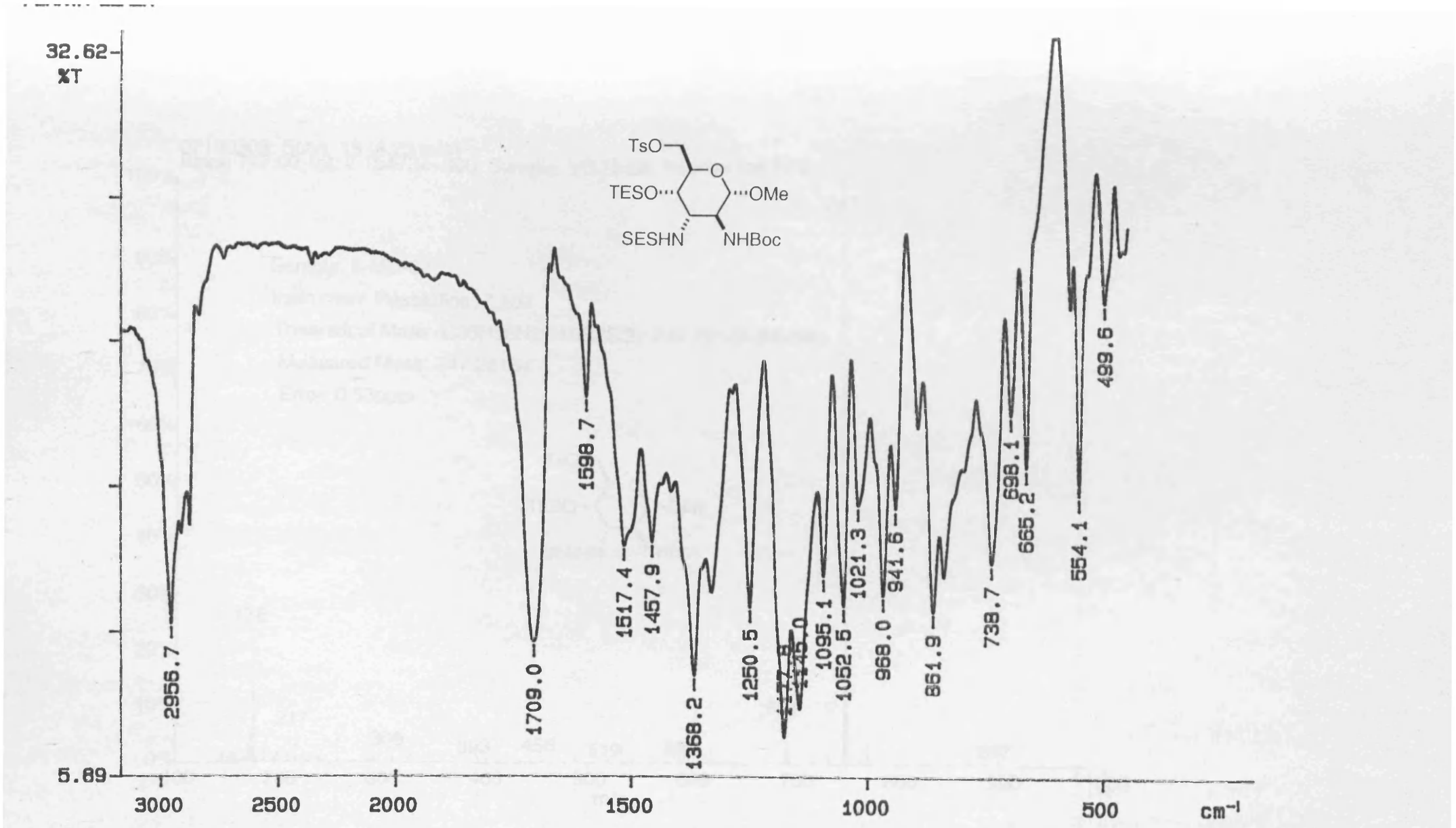




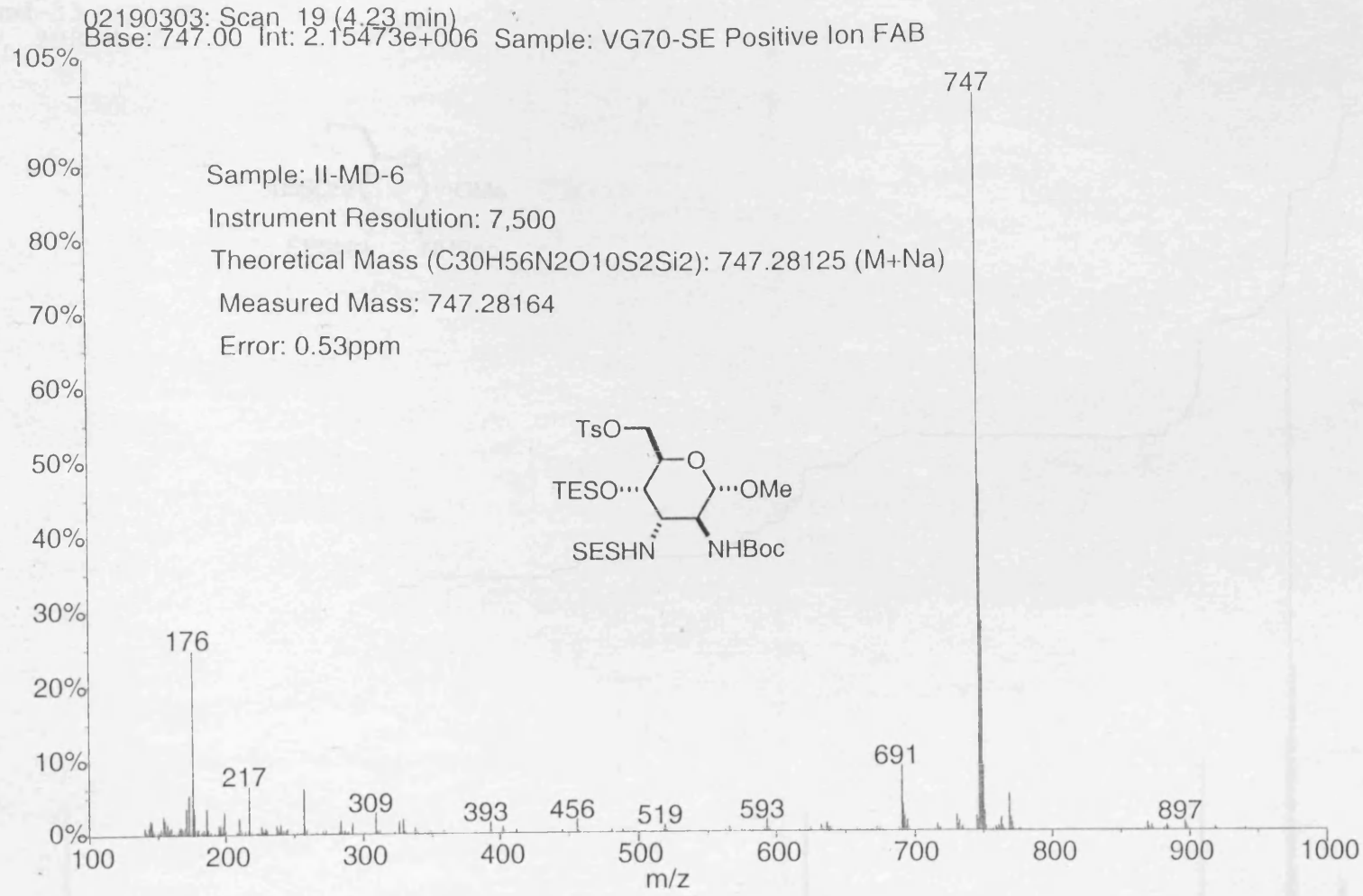
II-md-6
CDCl3, 298 K
HMQC



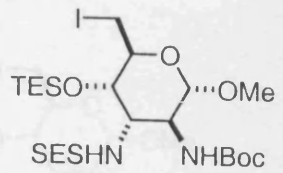




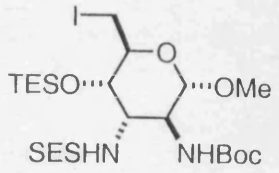
02/07/18 16: 16
X: 16 scans, 16.0cm-1, apod none, flat


02190303: Scan 19 (4.23 min)
Base: 747.00 Int: 2.15473e+006 Sample: VG70-SE Positive Ion FAB
Sample: II-MD-6
Instrument Resolution: 7,500
Theoretical Mass (C30H56N2O10S2Si2): 747.28125 (M+Na)
Measured Mass: 747.28164
Error: 0.53ppm
TsO
O
TESO
OMe
SESHN
NHBoc
747
691
897
176
217
309
393
456
519
593
105%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
100
200
300
400
500
600
700
800
900
1000
m/z

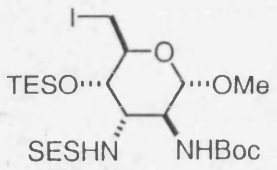
II-md-33
CDCl3, 298 K

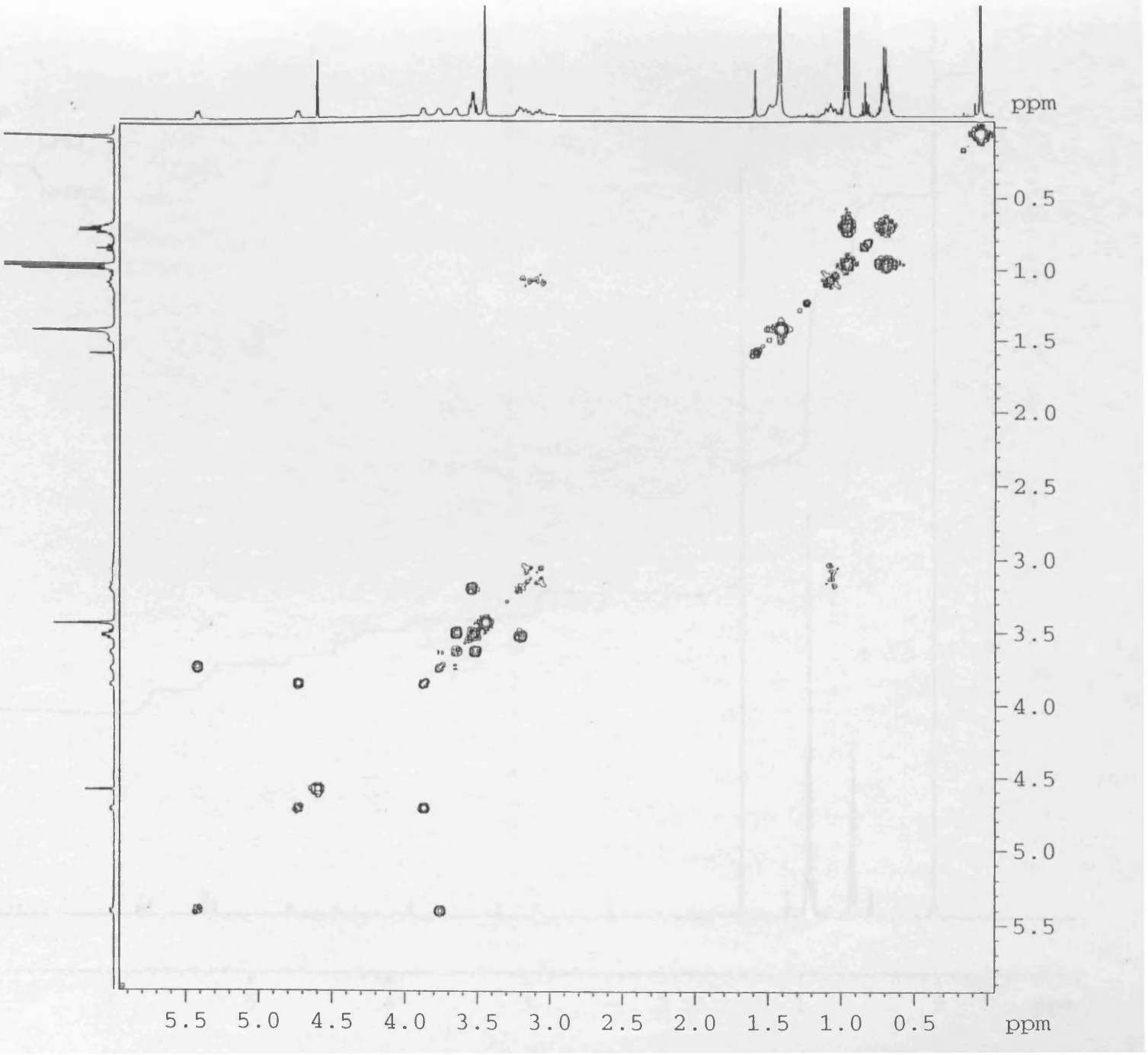


II-md-33
CDCl3, 298 K

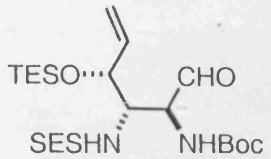


II-md-33
CDCl3, 298 K
COSY

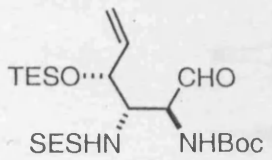




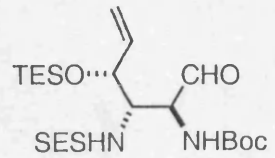
II-md-18
CDCl3, 298 K

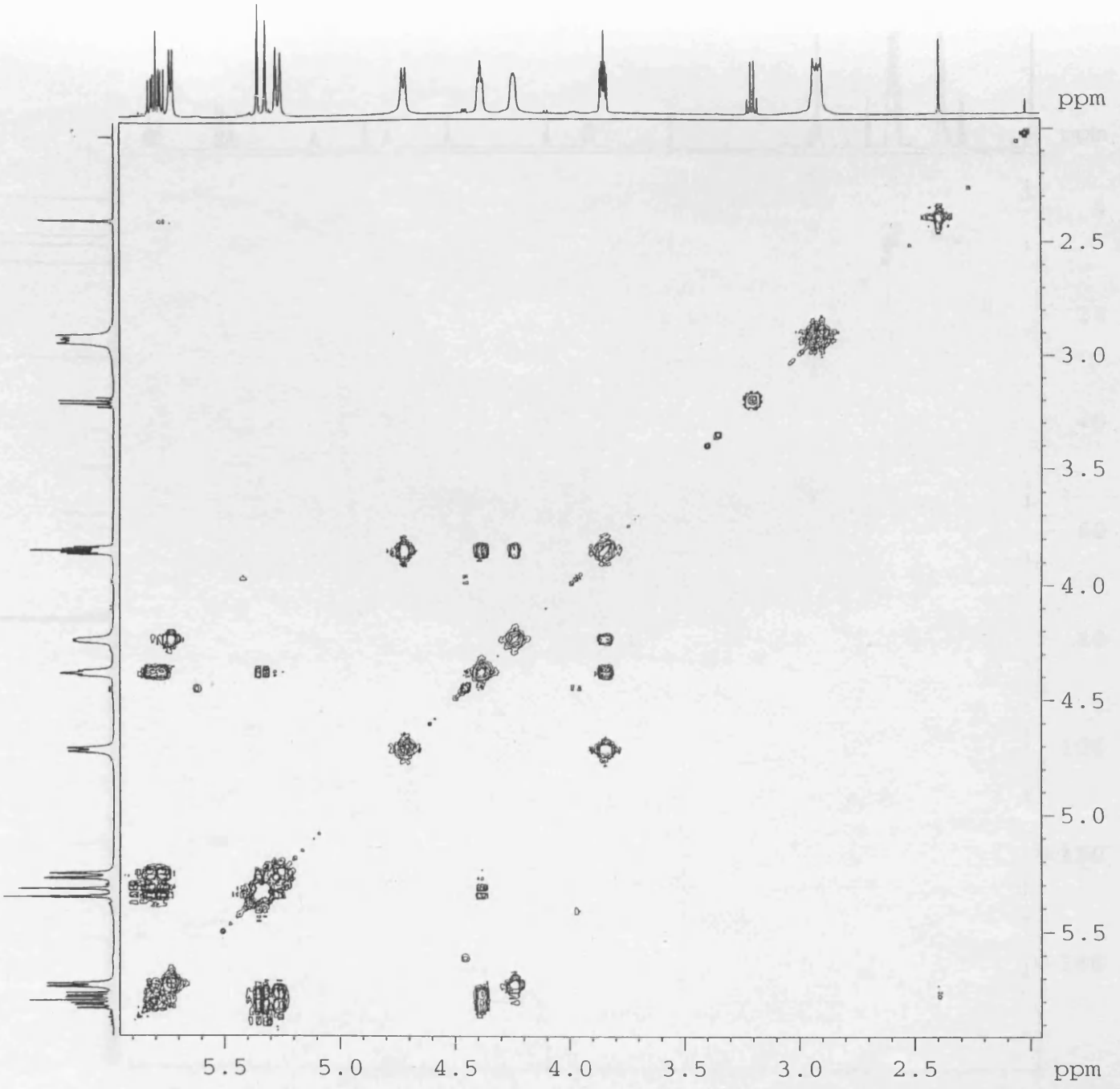


II-md-18
CDCl3, 298 K

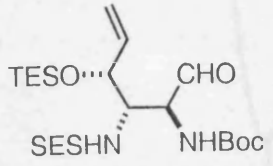


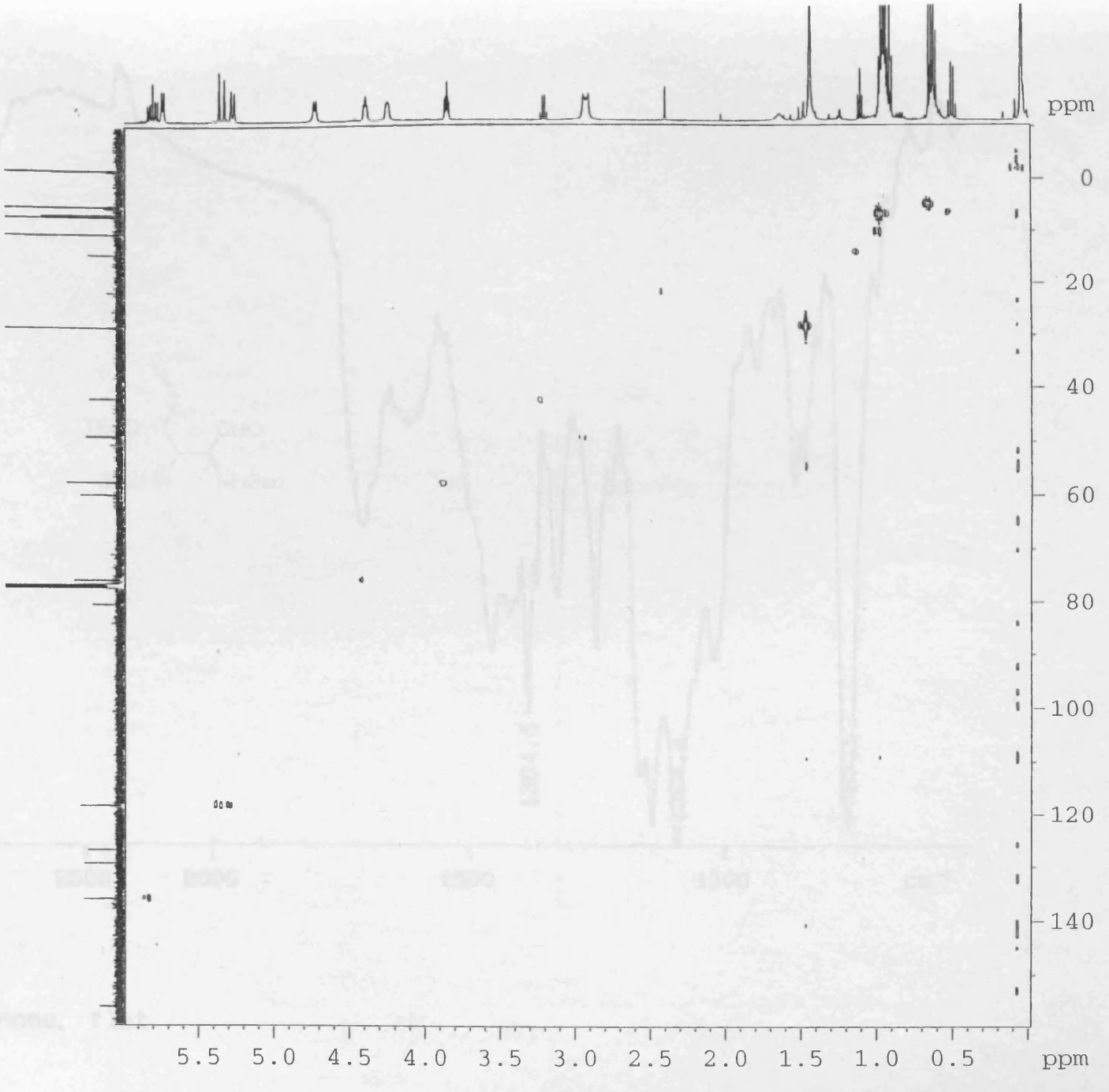
II-md-18
CDCl3, 298 K
COSY

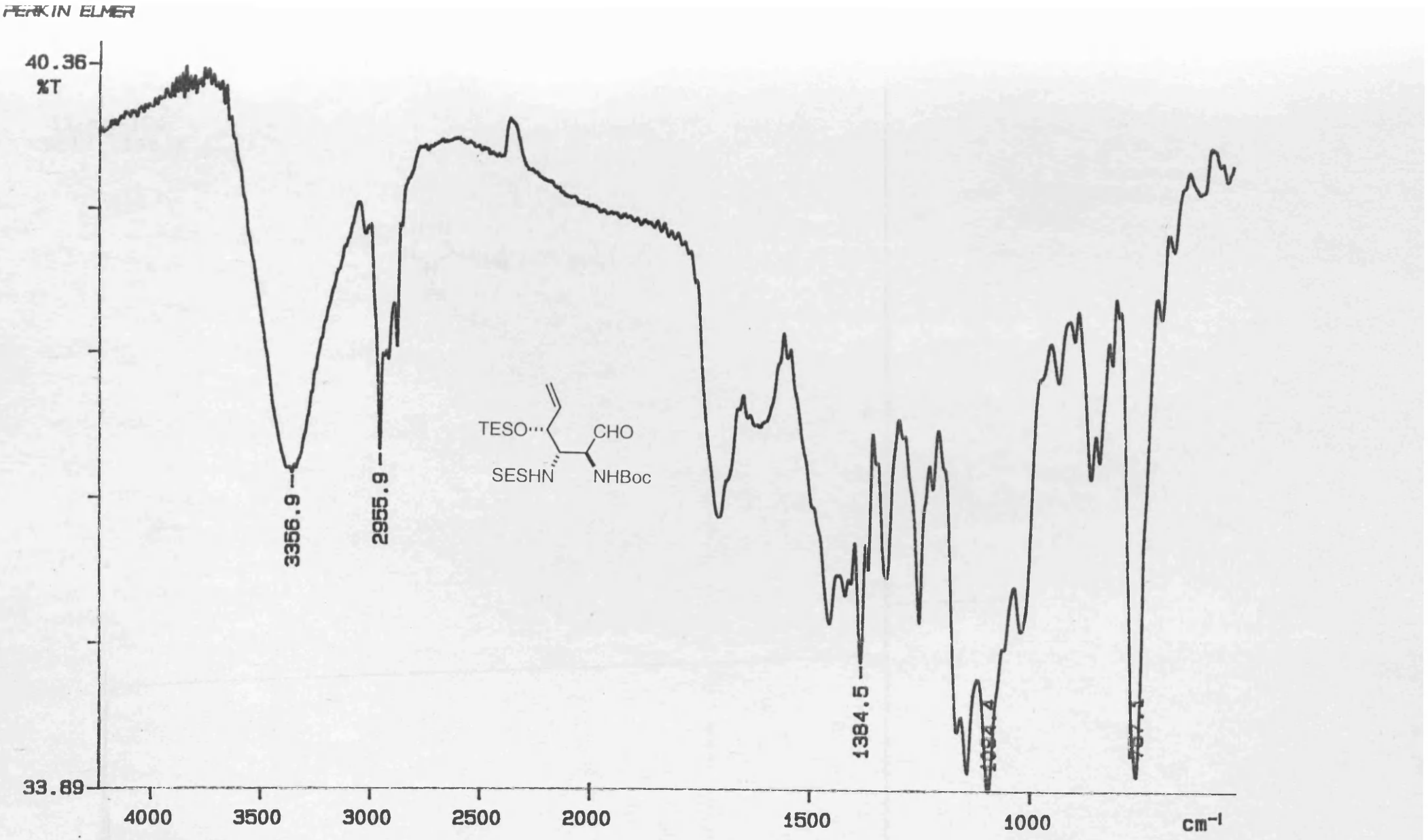




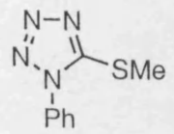
II-md-18
CDCl3, 298 K
HMQC



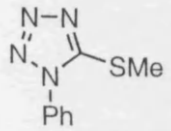


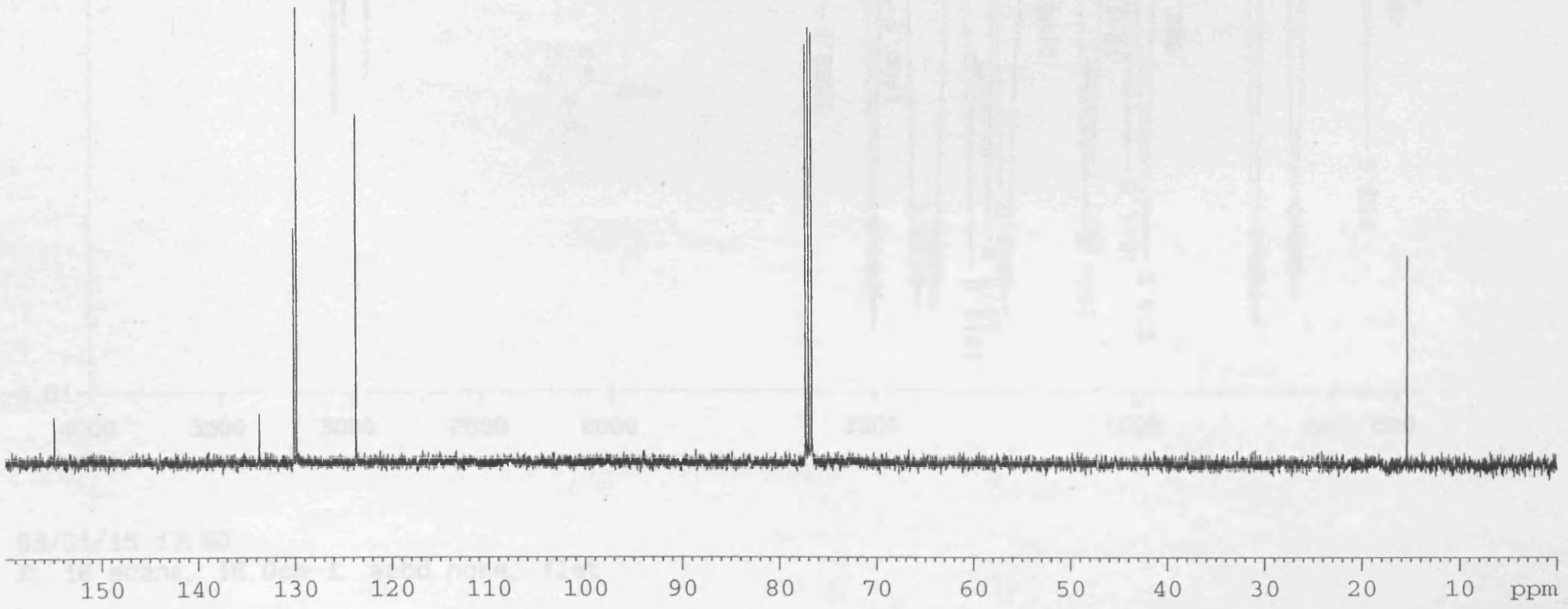

PERKIN ELMER
40.36
%T
33.89
3356.9
2955.9
1384.5
TESO
CHO
SESHN
NHBoc
4000
3500
3000
2500
2000
1500
1000
cm-1
02/07/18 14:26
X: 16 scans, 16.0cm-1, apod none, flat

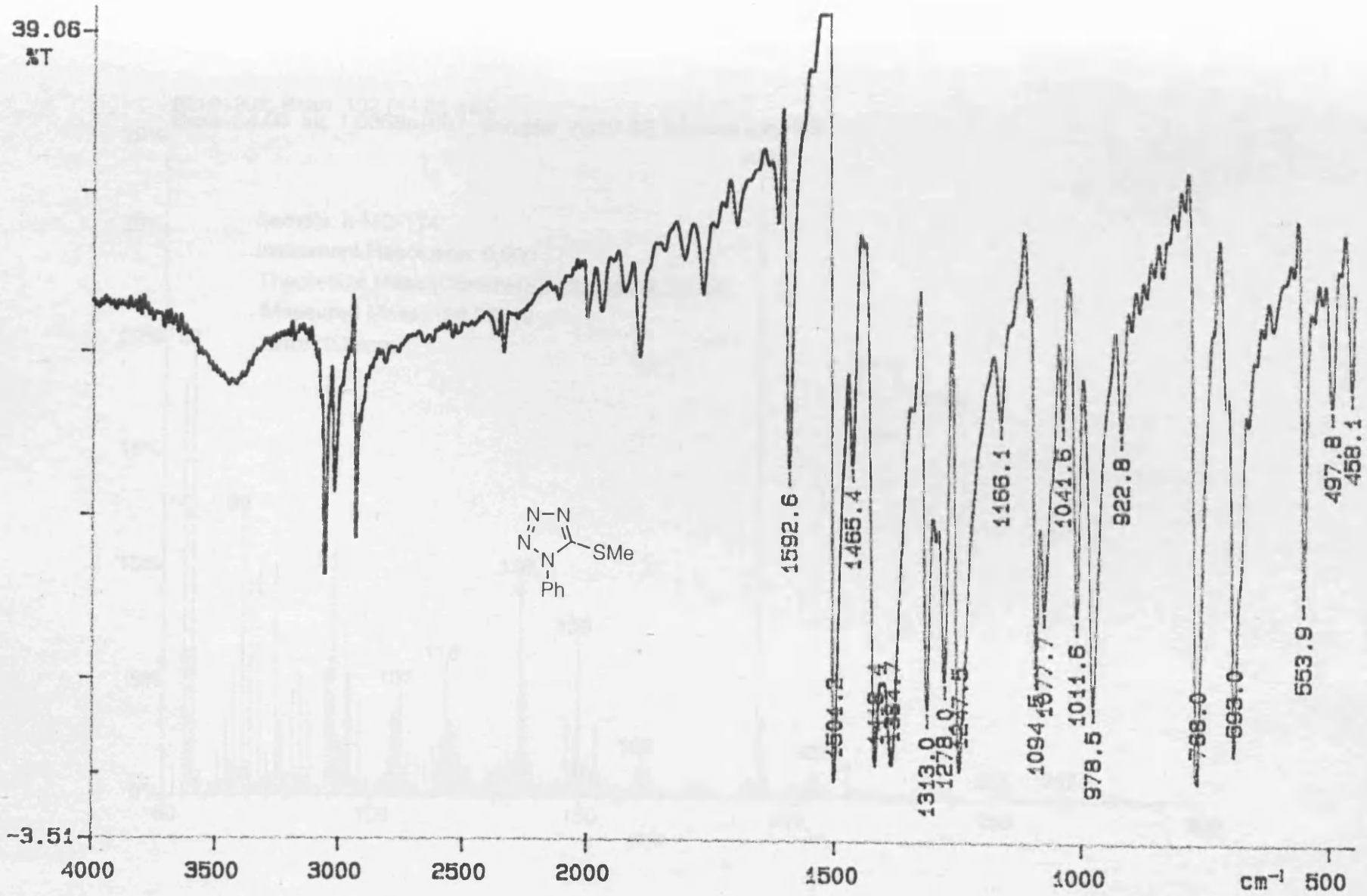
II-md-174
CDCl3, 298 K



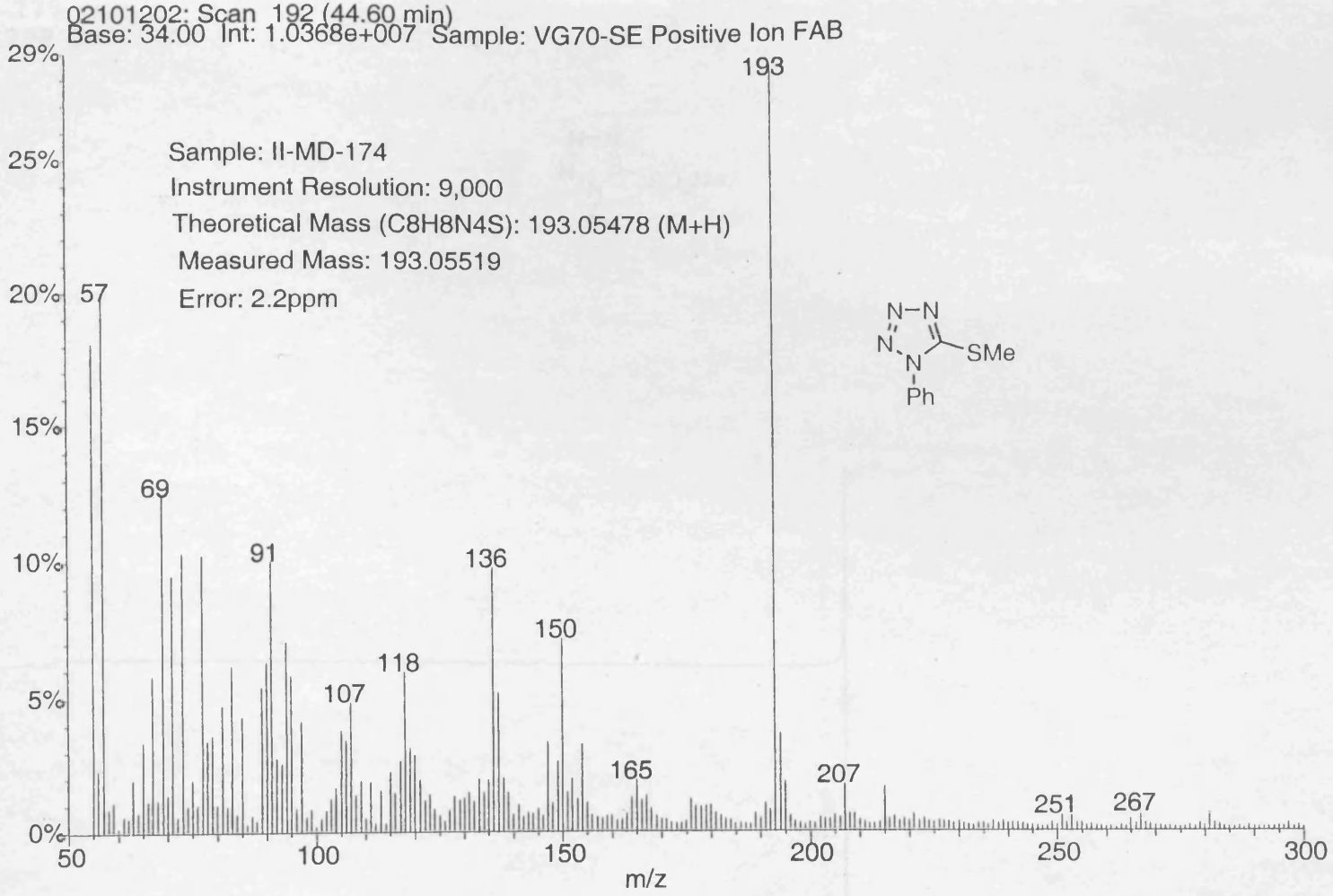
II-md-174
CDCl3, 298 K



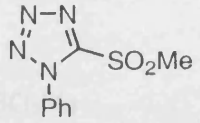


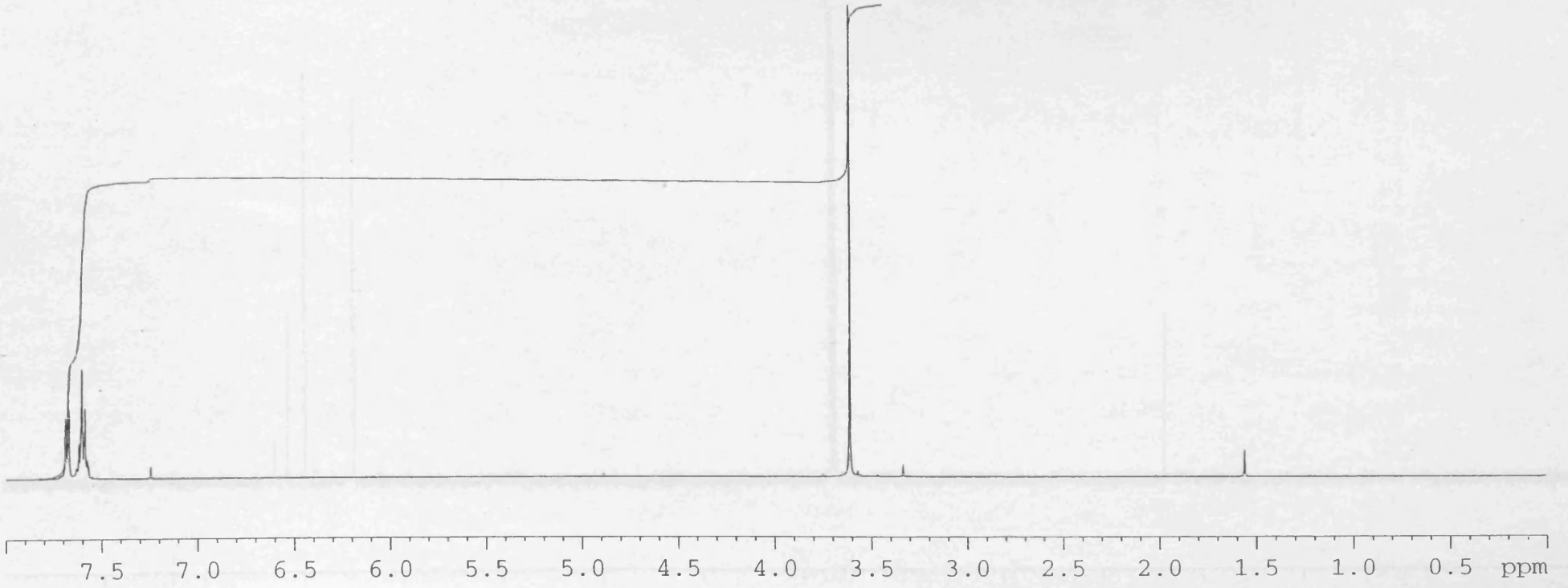


03/01/15 17:50
X: 16 scans, 16.0cm-1, apod none, flat

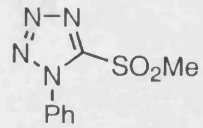

02101202: Scan 192 (44.60 min)
Base: 34.00 Int: 1.0368e+007 Sample: VG70-SE Positive Ion FAB
Sample: II-MD-174
Instrument Resolution: 9,000
Theoretical Mass (C8H8N4S): 193.05478 (M+H)
Measured Mass: 193.05519
Error: 2.2ppm
29%
25%
20%
15%
10%
5%
0%
193
57
69
91
136
150
118
107
165
207
251
267
50
100
150
200
250
300
m/z
N–N
N
N
SMe
Ph

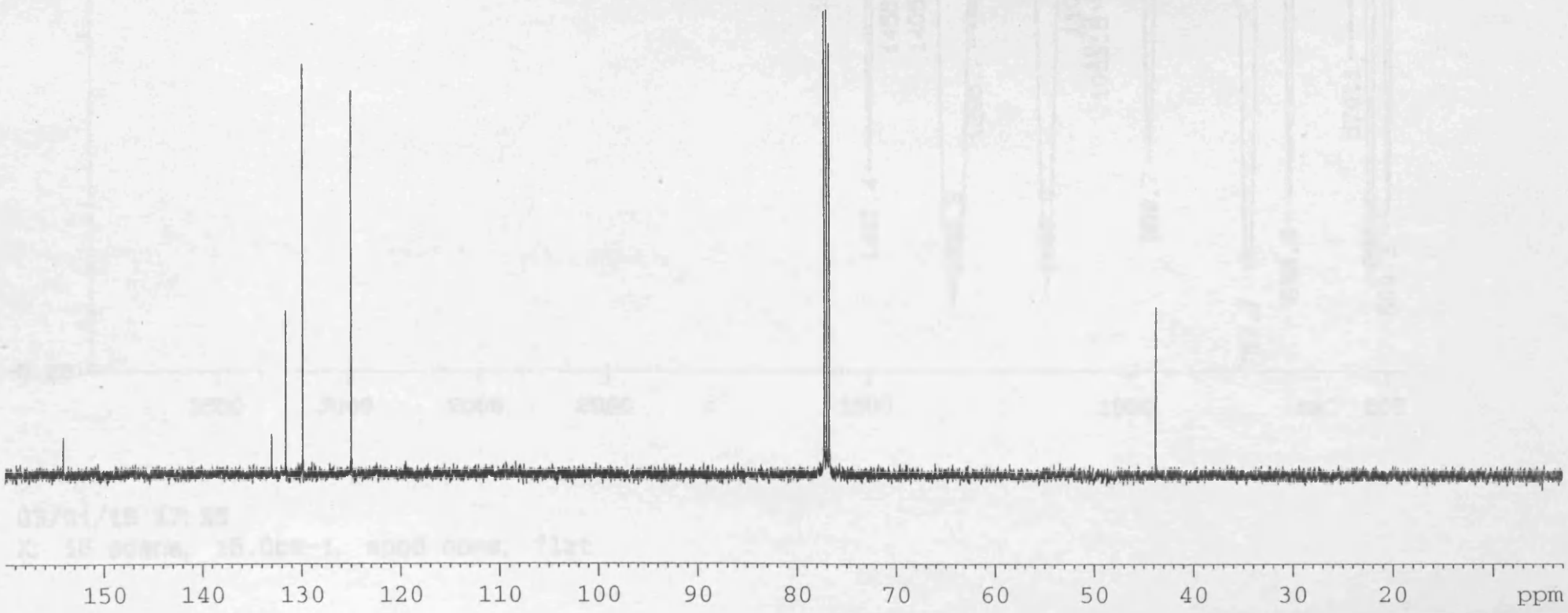
II-md-177
CDCl3, 298 K

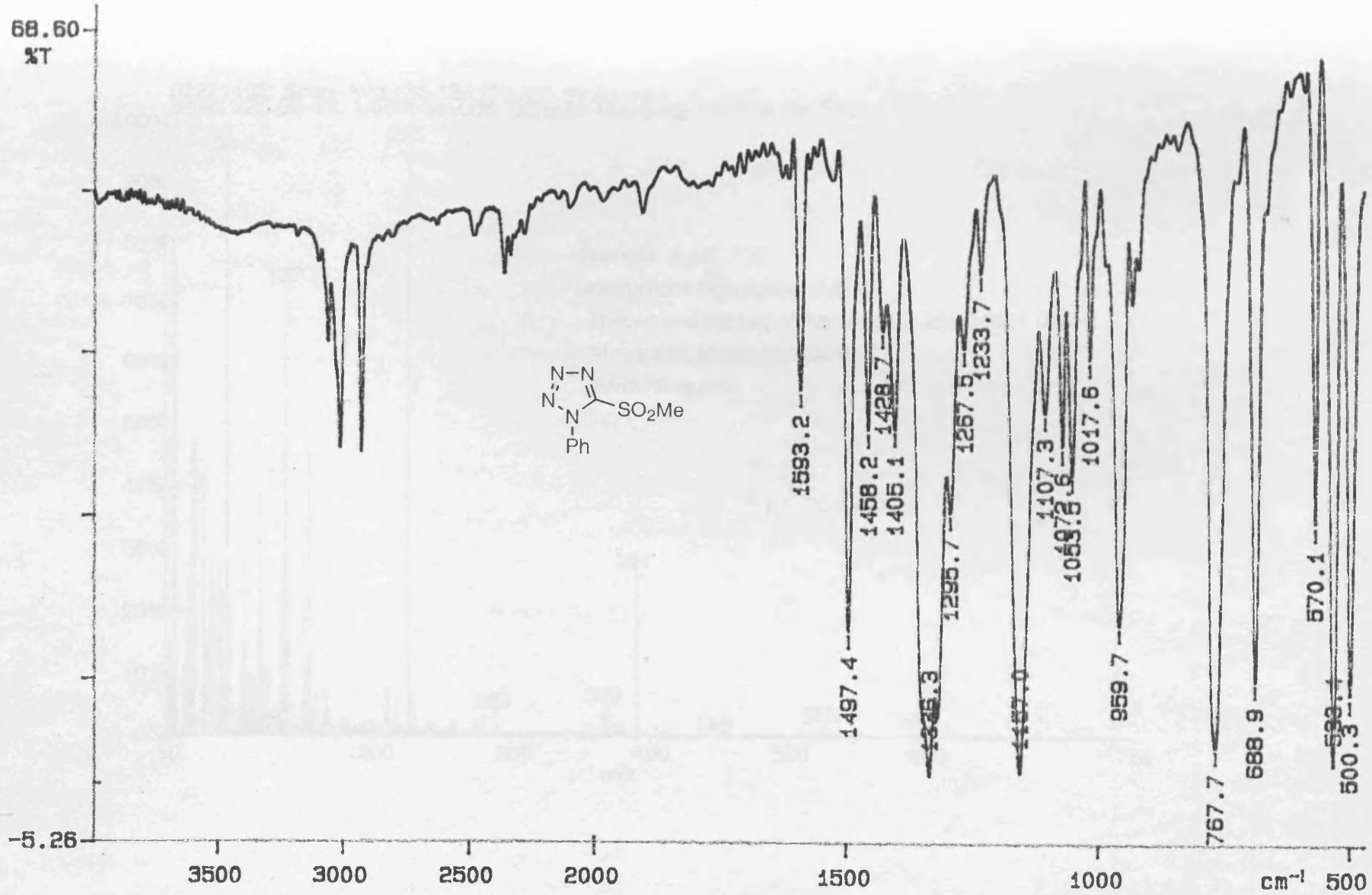




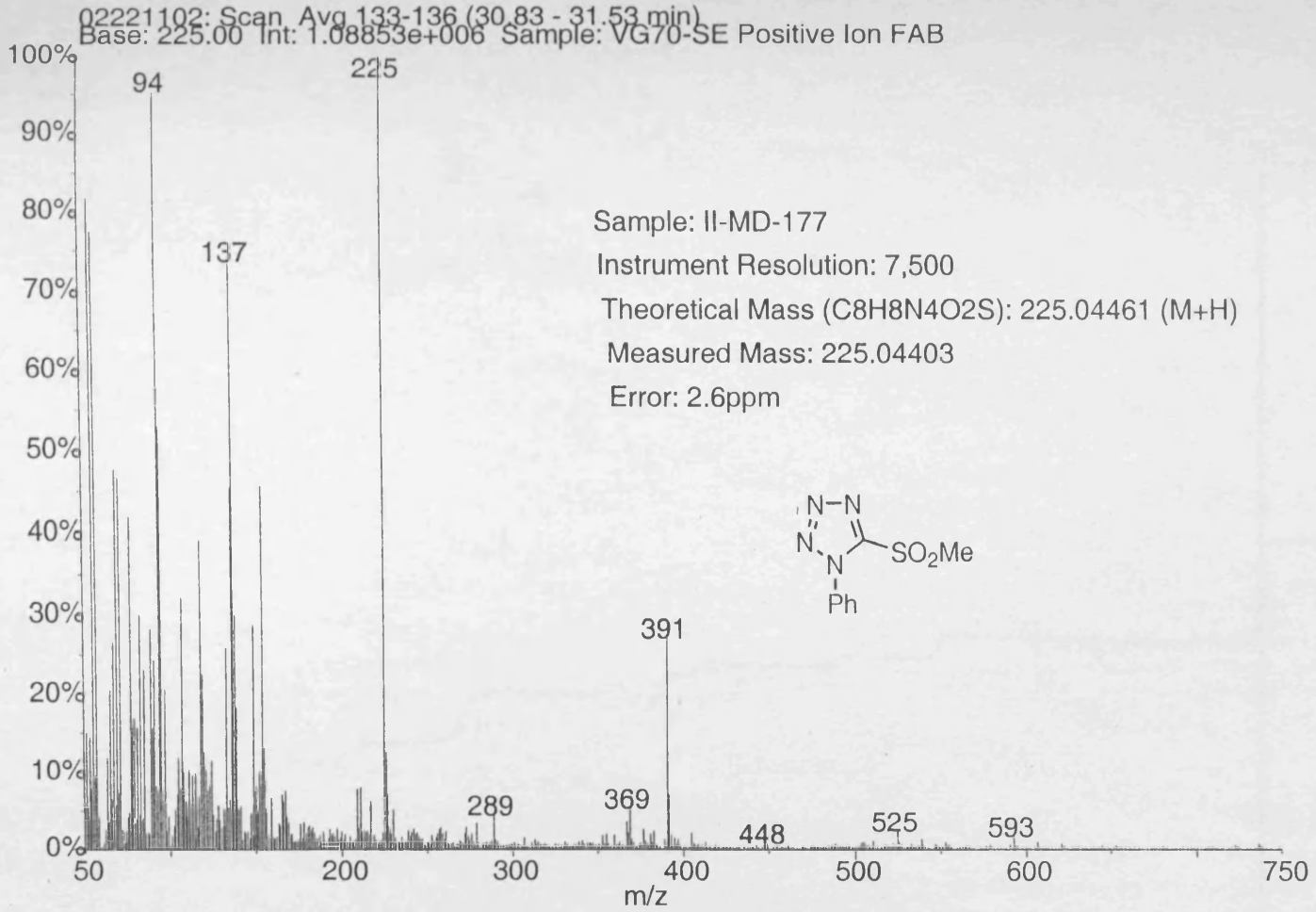
II-md-177
CDCl3, 298 K



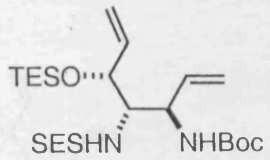




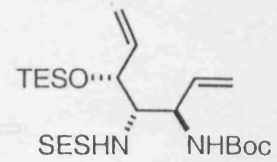
03/01/15 17:35
X: 16 scans, 16.0cm-1, apod none, flat


02221102: Scan Avg 133-136 (30.83 - 31.53 min)
Base: 225.00 Int: 1.08853e+006 Sample: VG70-SE Positive Ion FAB
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
94
225
137
391
289
369
448
525
593
50
200
300
400
500
600
750
m/z
Sample: II-MD-177
Instrument Resolution: 7,500
Theoretical Mass (C8H8N4O2S): 225.04461 (M+H)
Measured Mass: 225.04403
Error: 2.6ppm
N–N
N
N
SO2Me
Ph

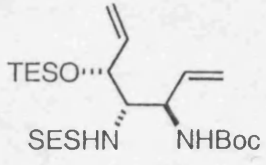
II-md-24
CDCl3, 298 K



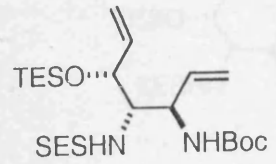
II-md-24
CDCl3, 298 K
DEPT

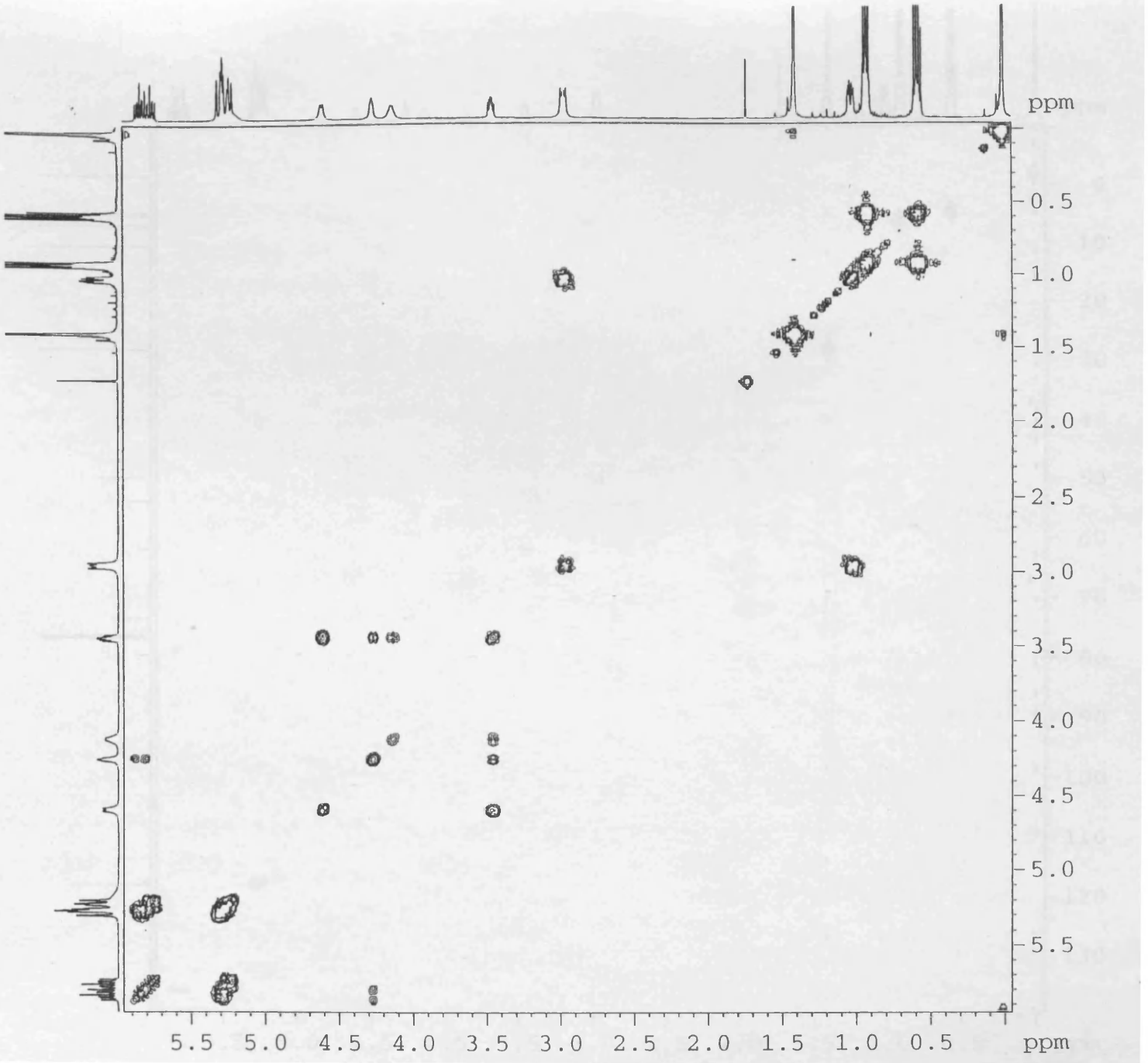


II-md-24
CDCl3, 298 K

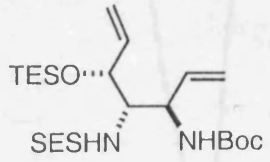


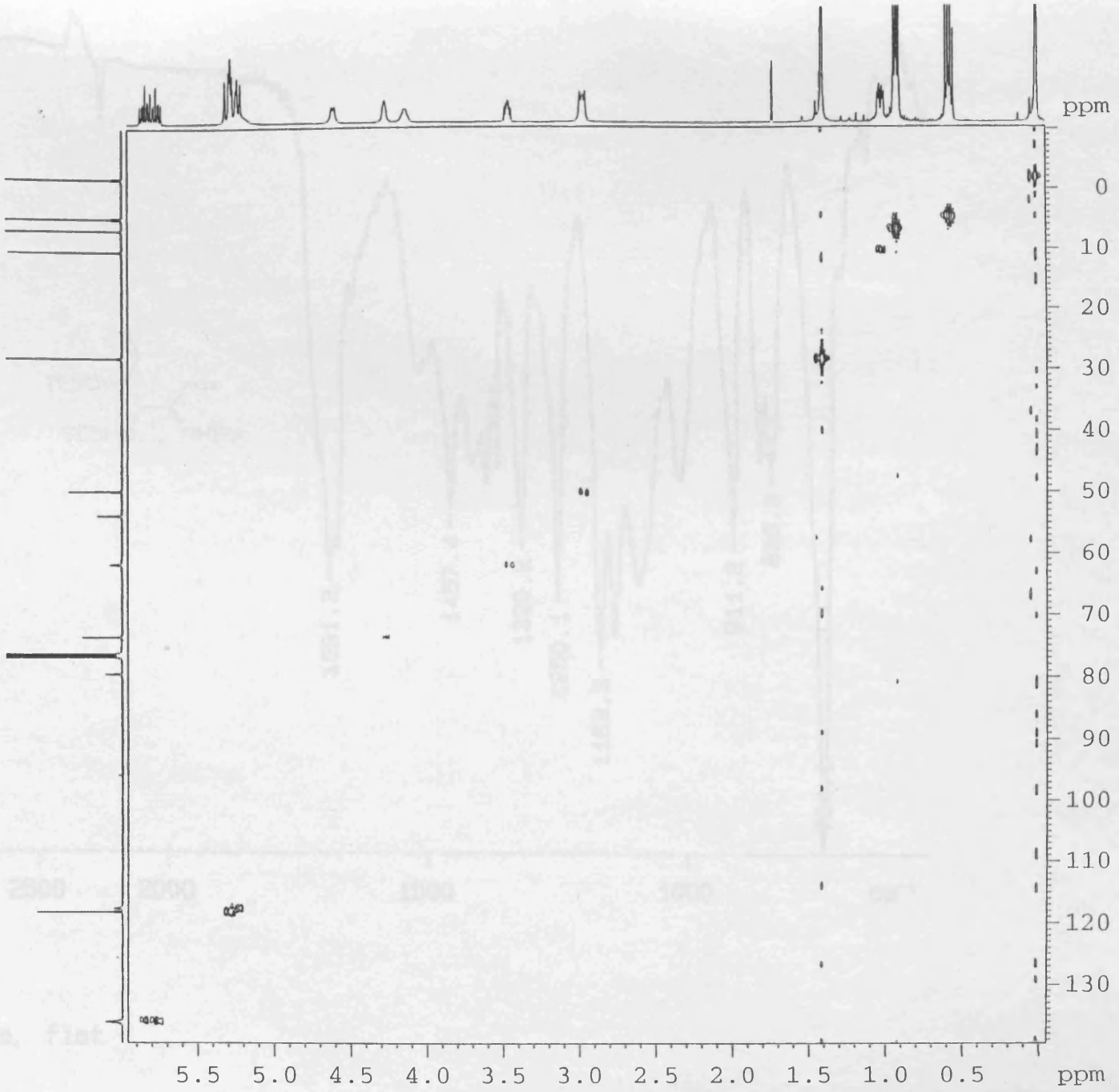
II-md-24
CDCl3, 298 K
COSY



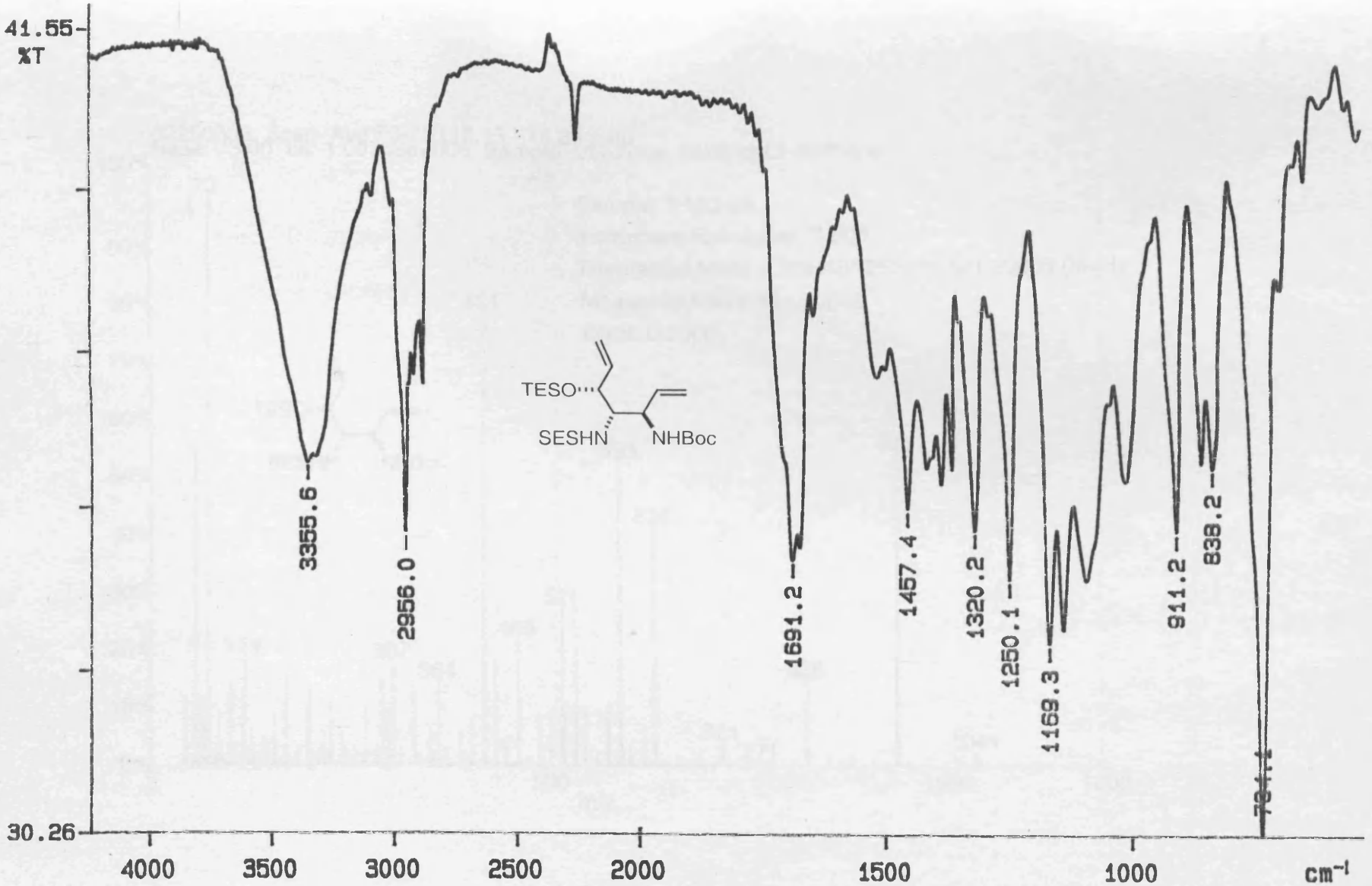


II-md-24
CDCl3, 298 K
HMQC

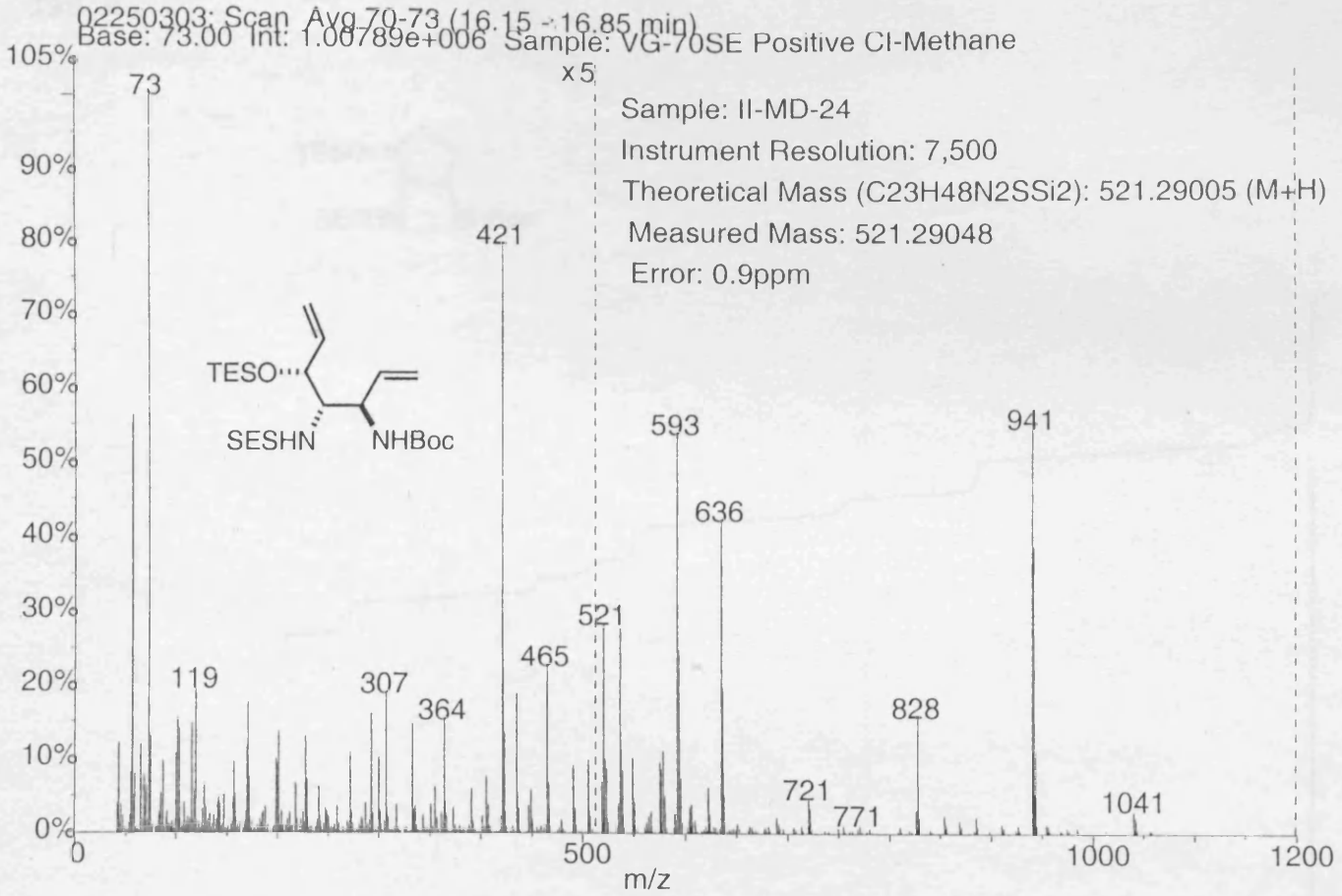




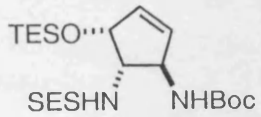
PERKIN ELMER

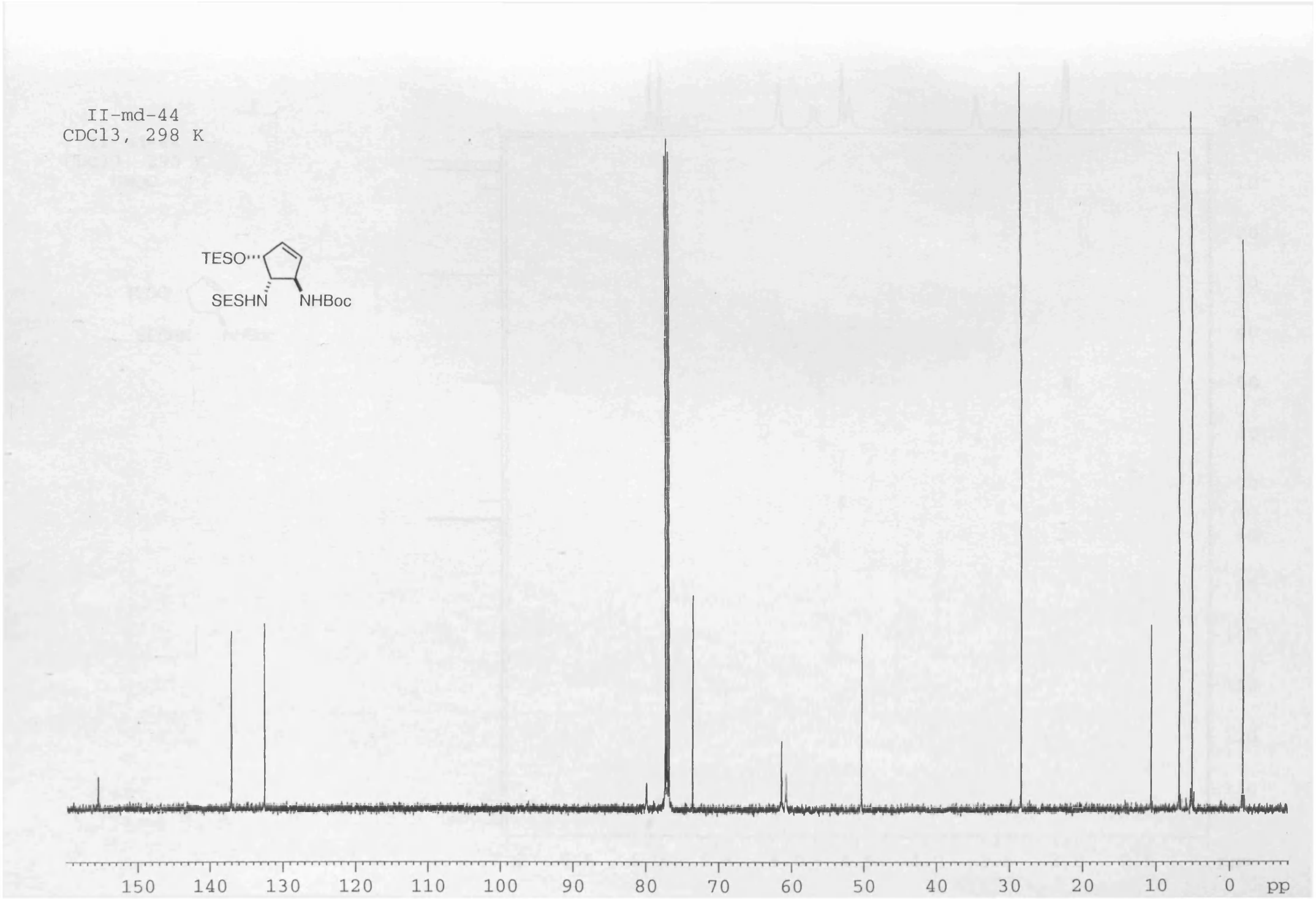


02/07/18 14:16
X: 16 scans, 16.0cm-1, apod none, flat

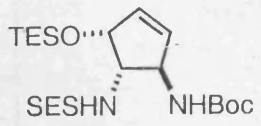

02250303: Scan Avg 70-73 (16.15 -:16.85 min)
Base: 73.00 Int: 1.00789e+006 Sample: VG-70SE Positive CI-Methane
x5
Sample: II-MD-24
Instrument Resolution: 7,500
Theoretical Mass (C23H48N2SSi2): 521.29005 (M+H)
Measured Mass: 521.29048
Error: 0.9ppm
TESO
SESHN
NHBoc
105%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
73
421
593
941
636
521
465
119
307
364
828
721
771
1041
0
500
1000
1200
m/z

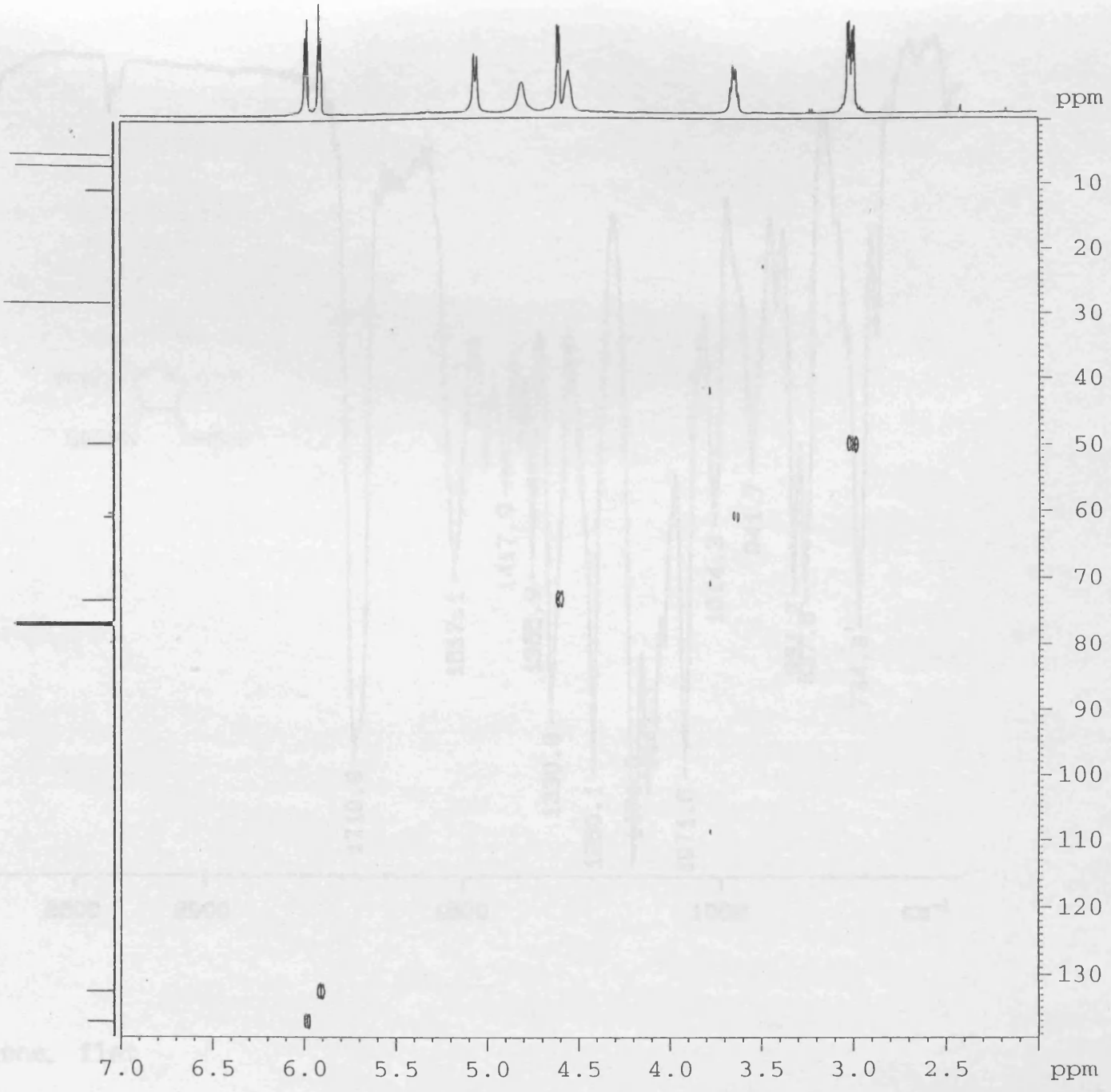
II-md-44
CDCl3, 298 K

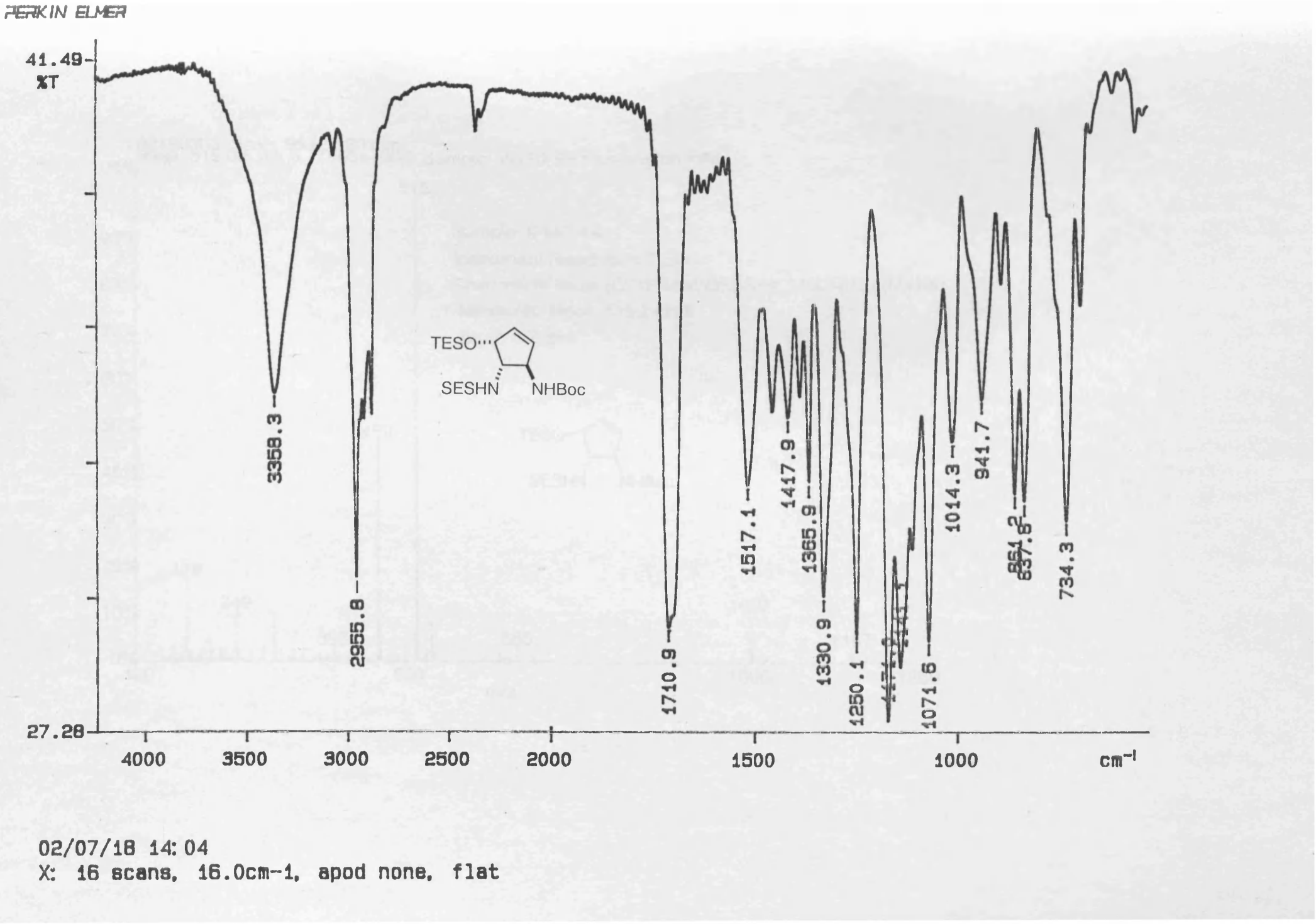


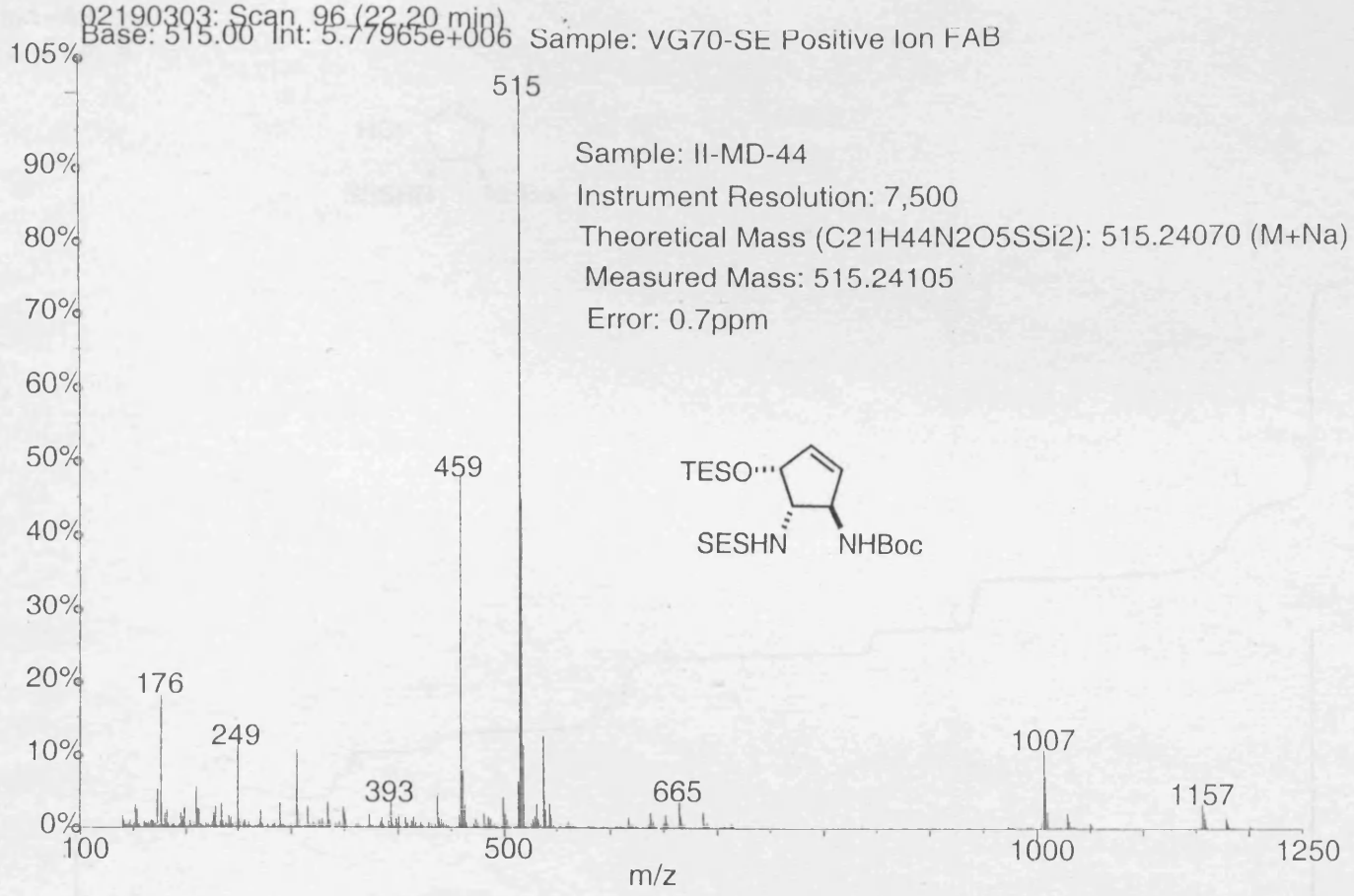

II-md-44
CDCl3, 298 K
TESO
SESHN
NHBoc
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
pp

II-md-44
CDC13, 298 K
HMQC

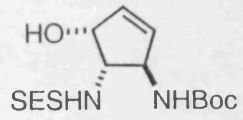




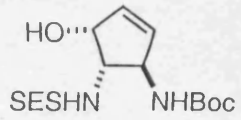

PERKIN ELMER
41.49
%T
27.28
3358.3
2955.8
1710.9
1517.1
1417.9
1365.9
1330.9
1250.1
1071.6
1014.3
941.7
851.2
837.8
734.3
TESO
SESHN
NHBoc
4000
3500
3000
2500
2000
1500
1000
cm-1
02/07/18 14:04
X: 16 scans, 16.0cm-1, apod none, flat


02190303: Scan 96 (22.20 min)
Base: 515.00 Int: 5.77965e+006 Sample: VG70-SE Positive Ion FAB
105%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
515
459
176
249
393
665
1007
1157
100
500
1000
1250
m/z
Sample: II-MD-44
Instrument Resolution: 7,500
Theoretical Mass (C21H44N2O5SSi2): 515.24070 (M+Na)
Measured Mass: 515.24105
Error: 0.7ppm
TESO
SESHN
NHBoc

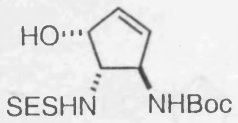
II-md-49
CDCl3, 298 K

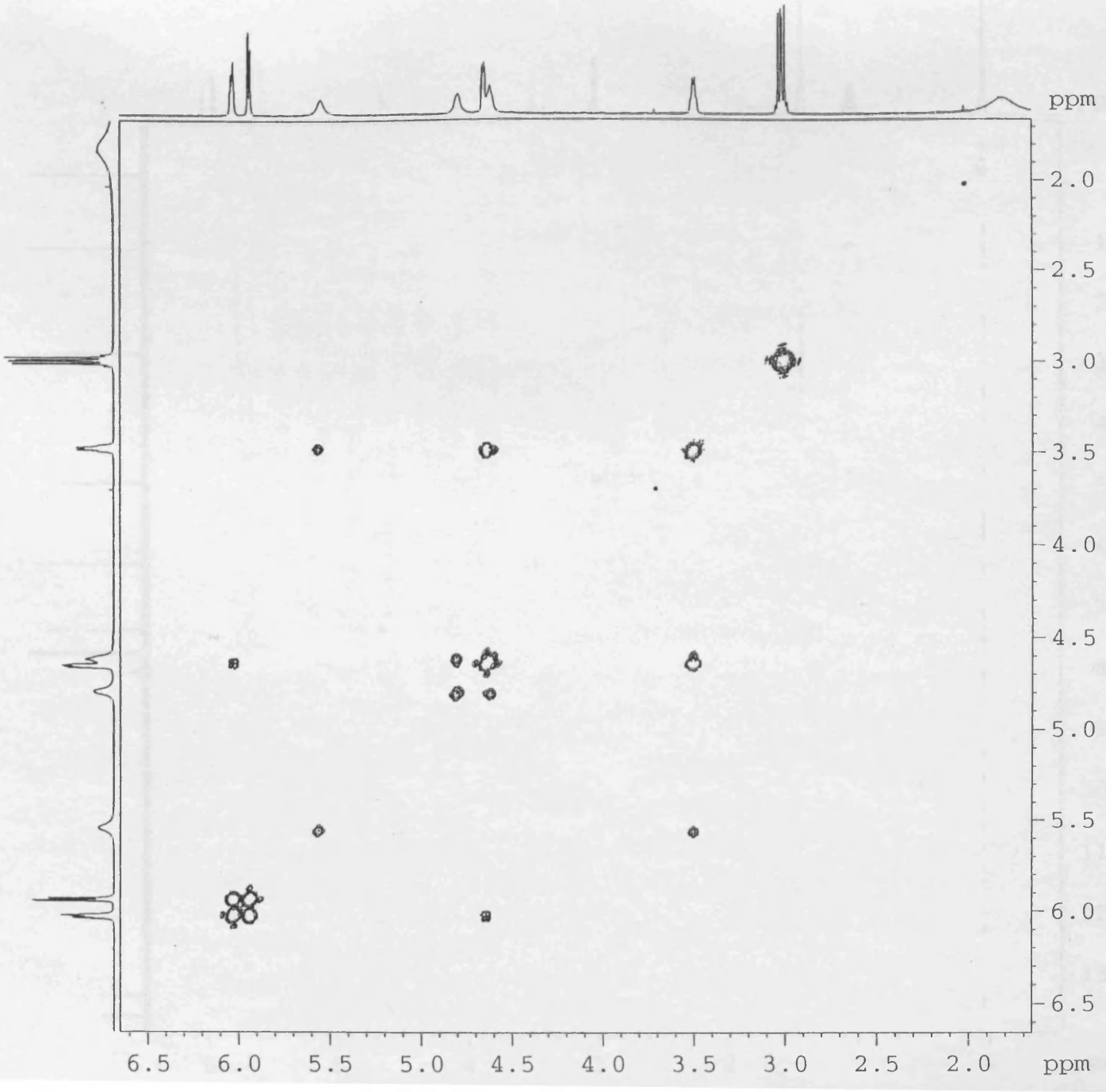


II-md-49
CDCl3, 298 K

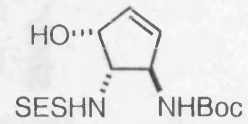


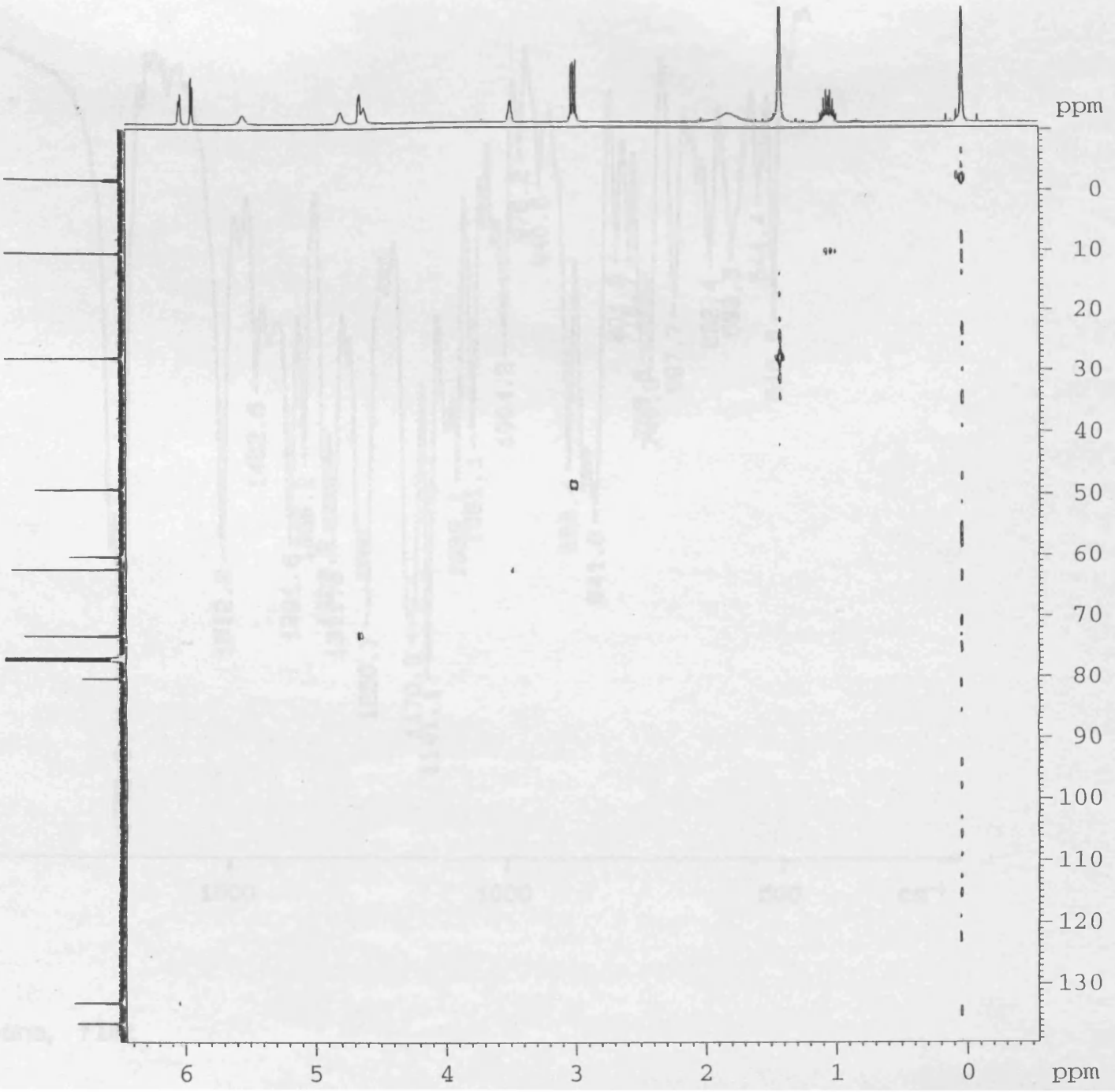
II-md-49
CDCl3, 298 K
COSY

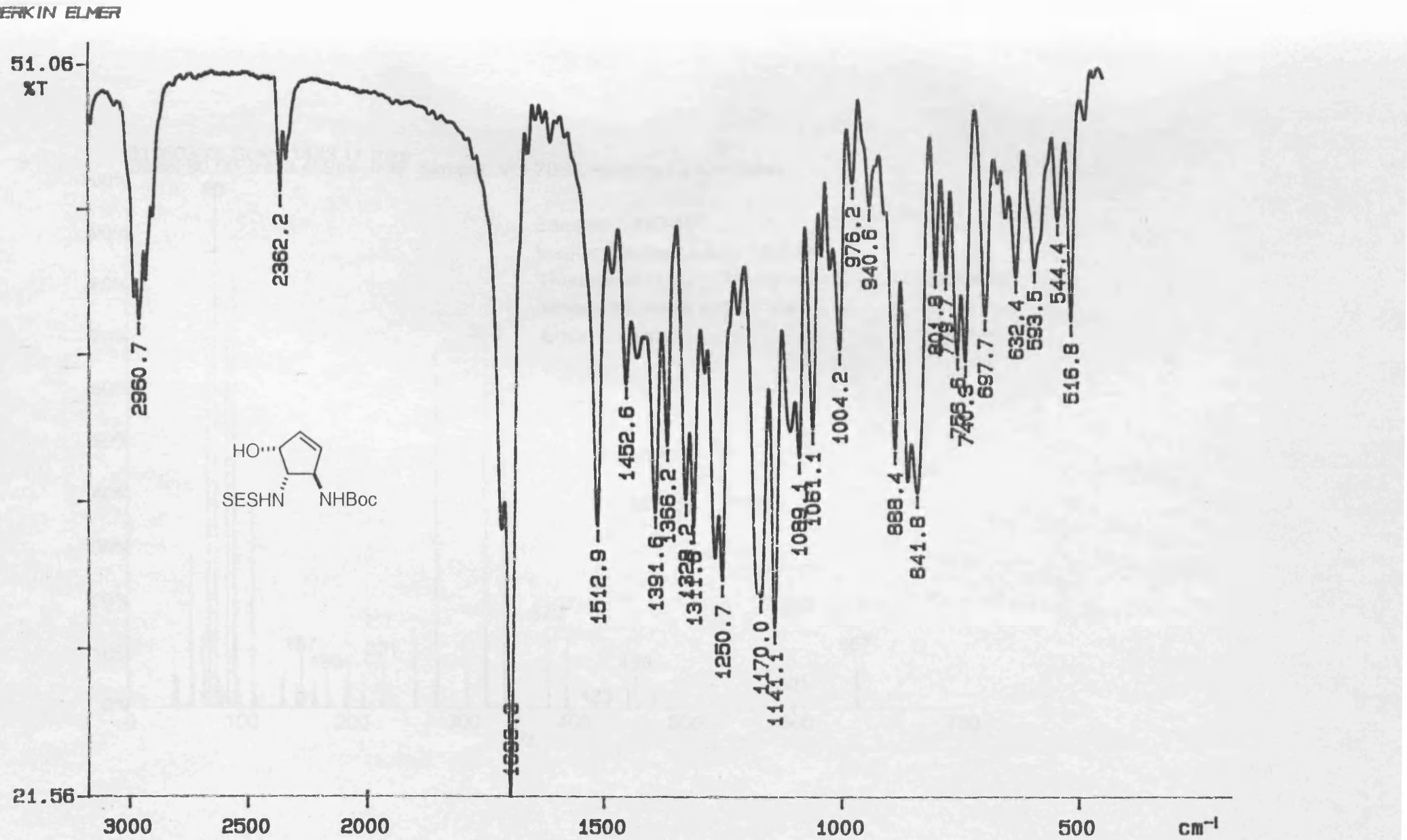




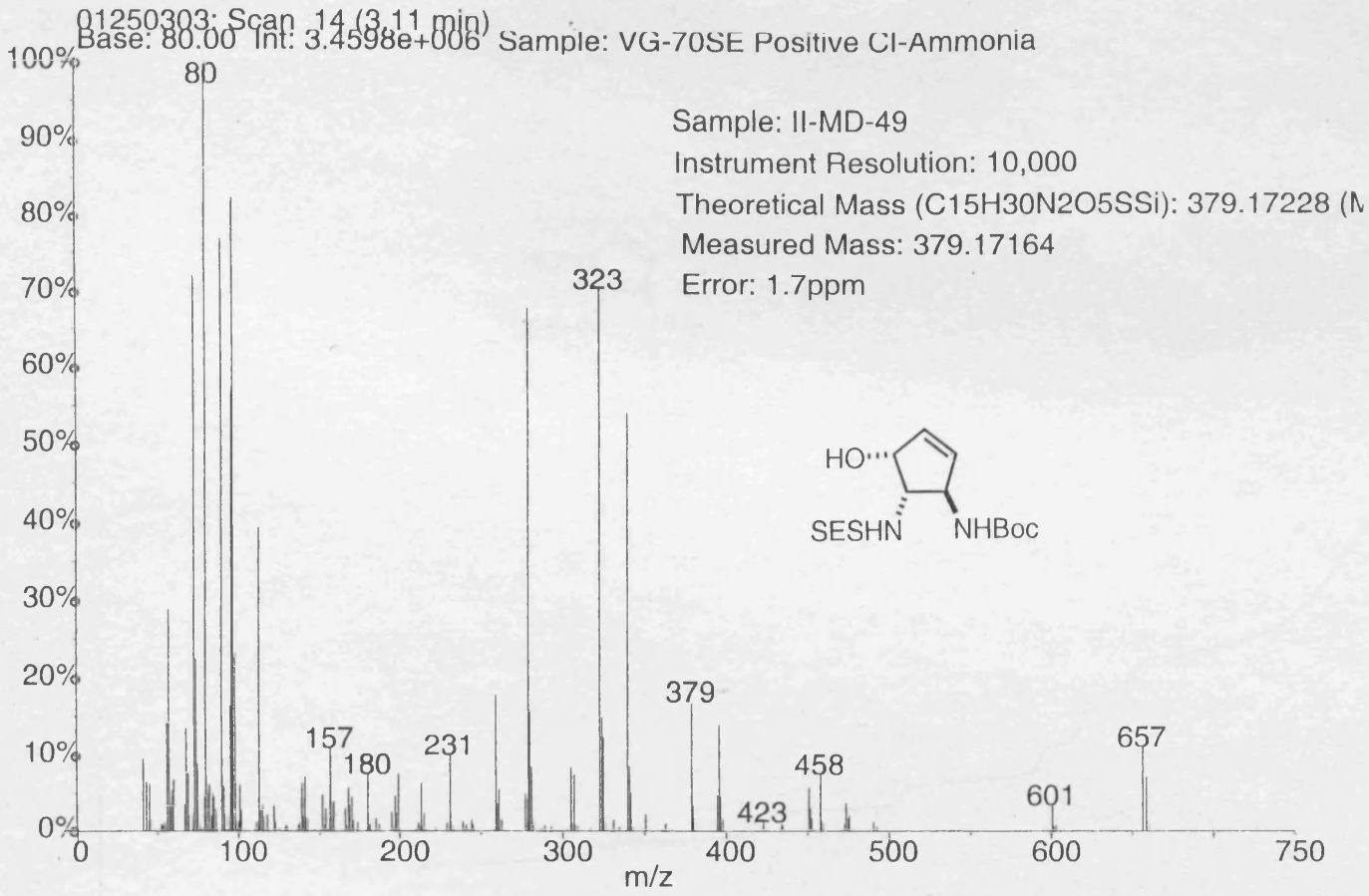
II-md-49
CDCl3, 298 K
HMQC



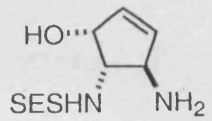


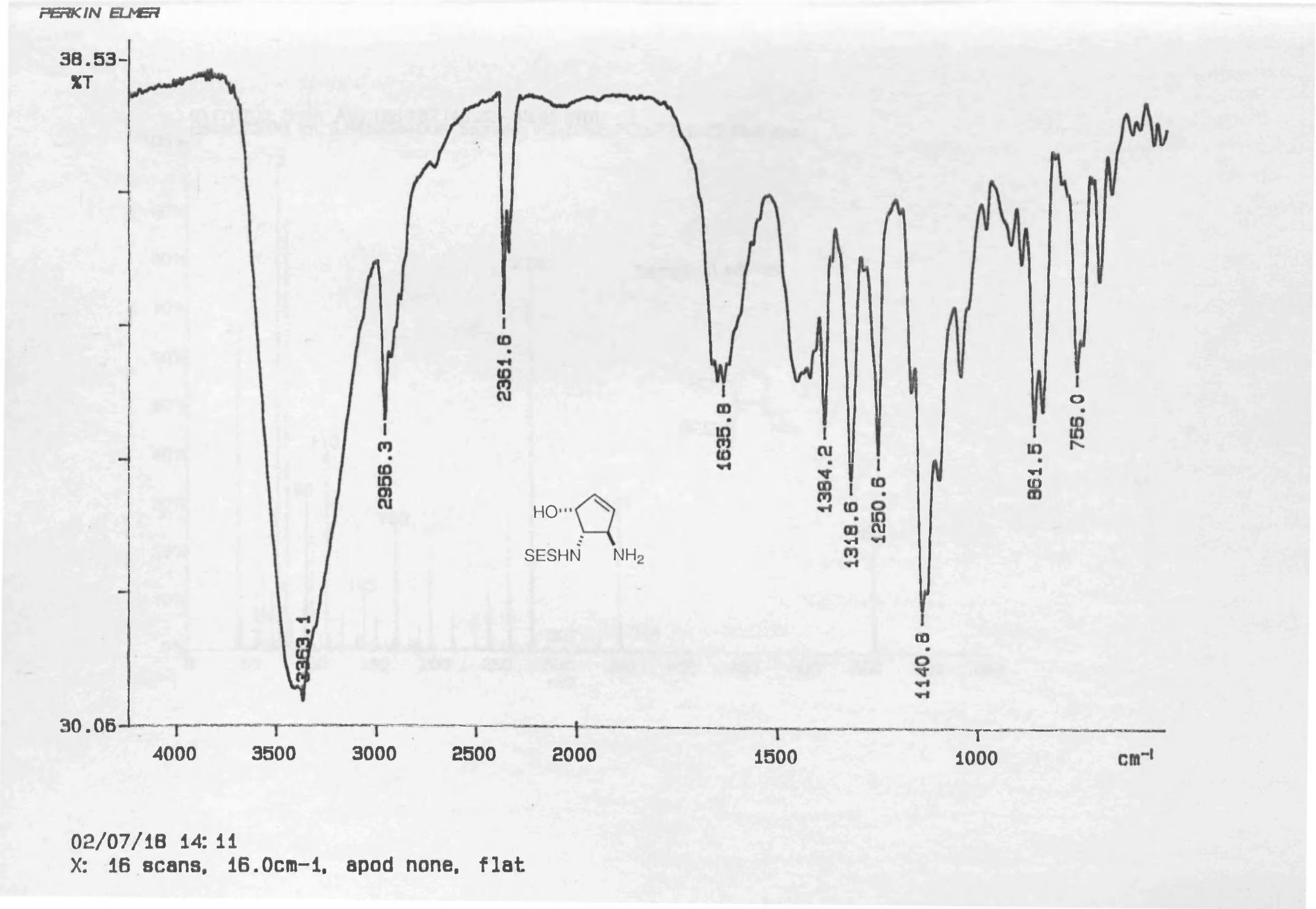


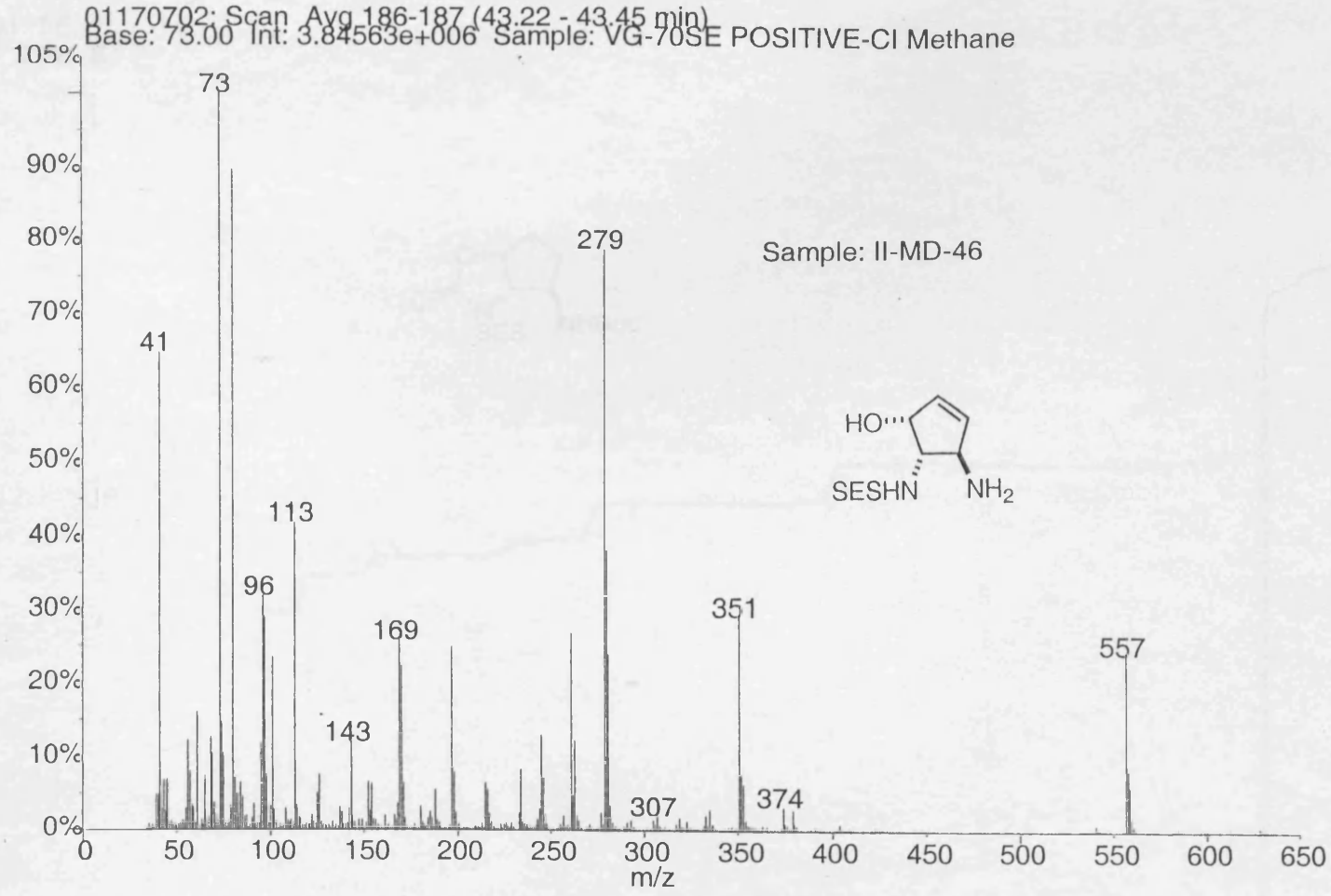
02/07/18 14:55
X: 16 scans, 16.0cm-1, apod none, flat


01250303: Scan 14 (3.11 min)
Base: 80.00 Int: 3.4598e+006 Sample: VG-70SE Positive CI-Ammonia
Sample: II-MD-49
Instrument Resolution: 10,000
Theoretical Mass (C15H30N2O5SSi): 379.17228 (M
Measured Mass: 379.17164
Error: 1.7ppm
HO
SESHN
NHBoc
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
80
323
379
157
180
231
423
458
601
657
0
100
200
300
400
500
600
750
m/z

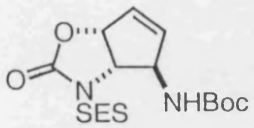
II-md-46
CDCl3, 298 K



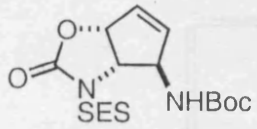

PERKIN ELMER
38.53
%T
30.06
3363.1
2956.3
2361.6
1635.8
1384.2
1318.6
1250.6
1140.8
861.5
755.0
HO
SESHN
NH2
4000
3500
3000
2500
2000
1500
1000
cm-1
02/07/18 14:11
X: 16 scans, 16.0cm-1, apod none, flat

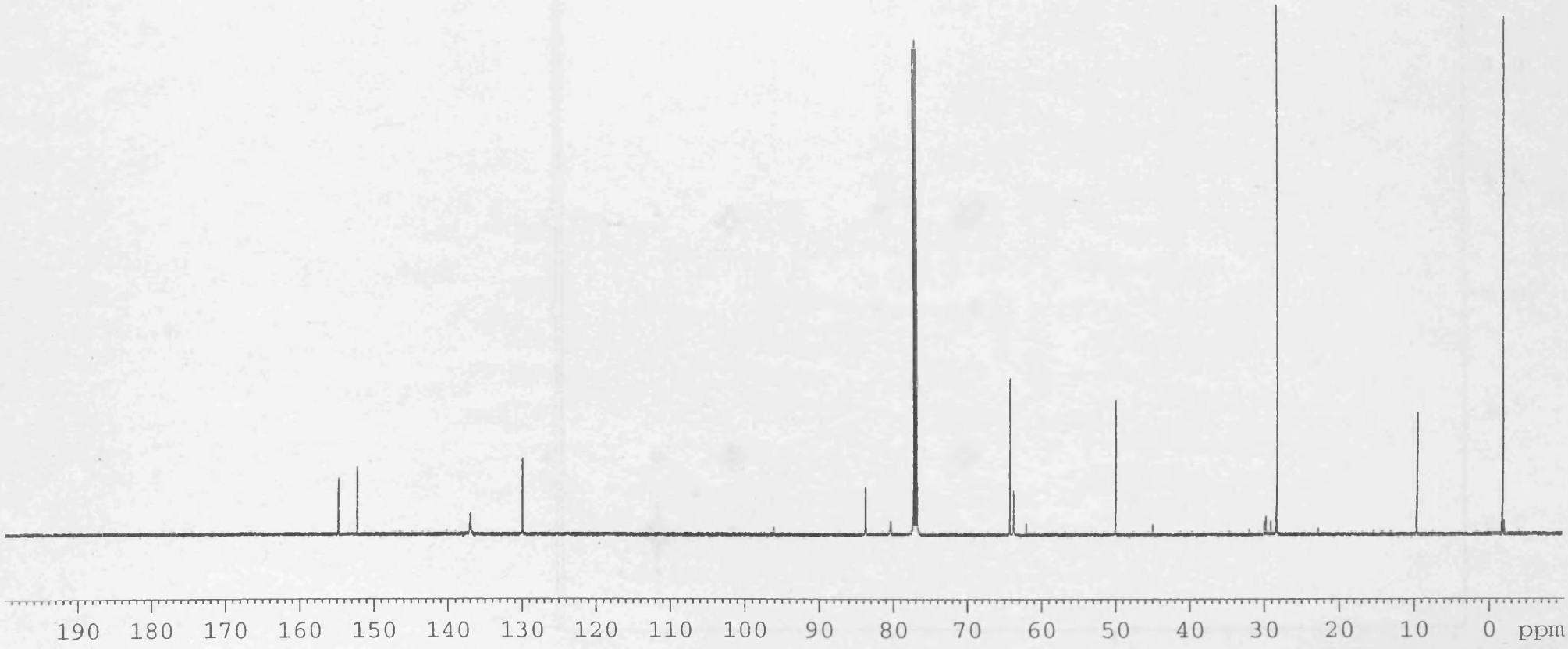

01170702: Scan Avg 186-187 (43.22 - 43.45 min)
Base: 73.00 Int: 3.84563e+006 Sample: VG-70SE POSITIVE-CI Methane
105%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
73
279
41
113
96
169
143
351
557
307
374
0
50
100
150
200
250
300
350
400
450
500
550
600
650
m/z
Sample: II-MD-46
HO
SESHN
NH2

II-md-56
CDCl3, 298 K

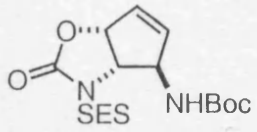


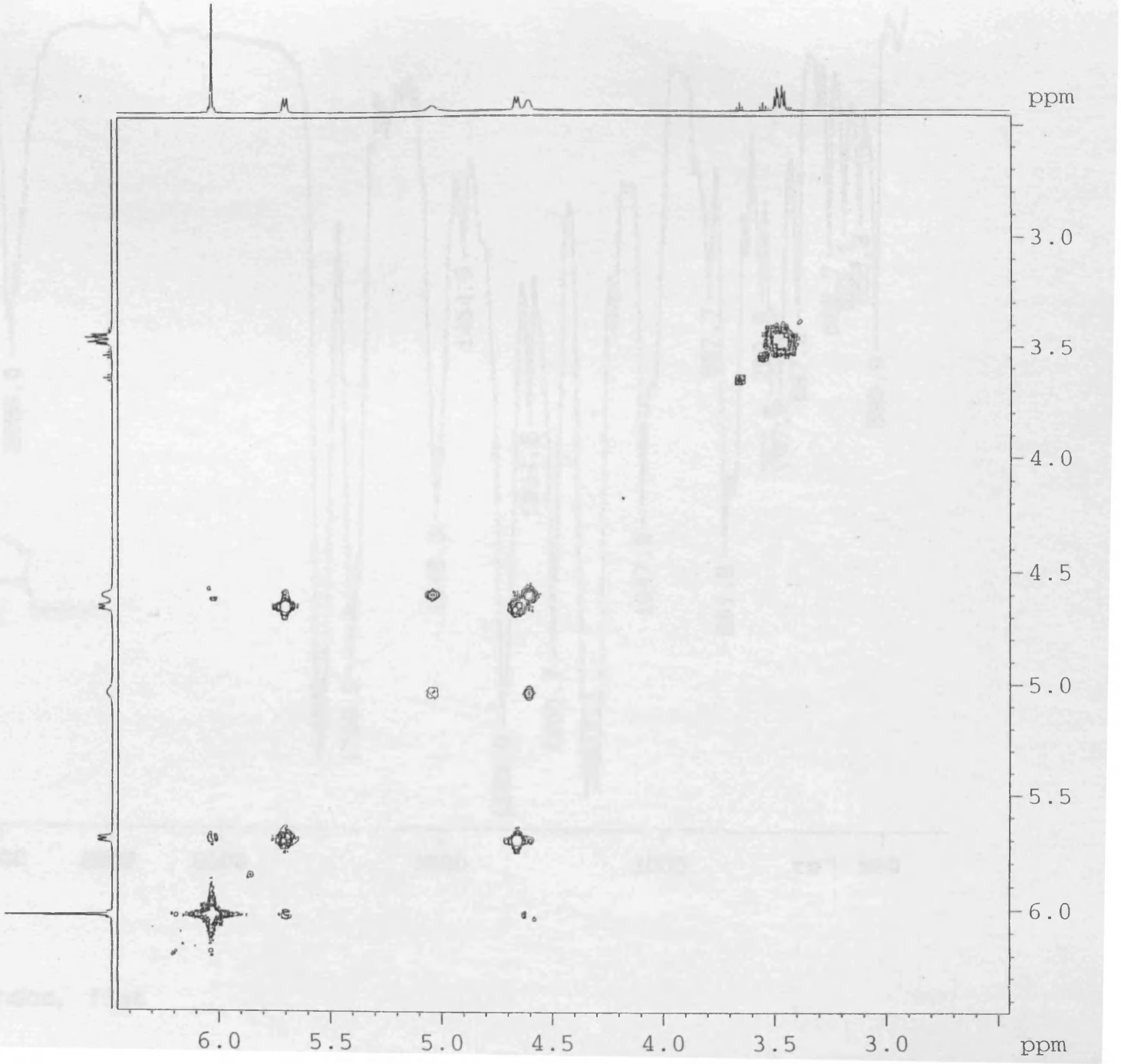
II-md-56
CDCl3, 298 K

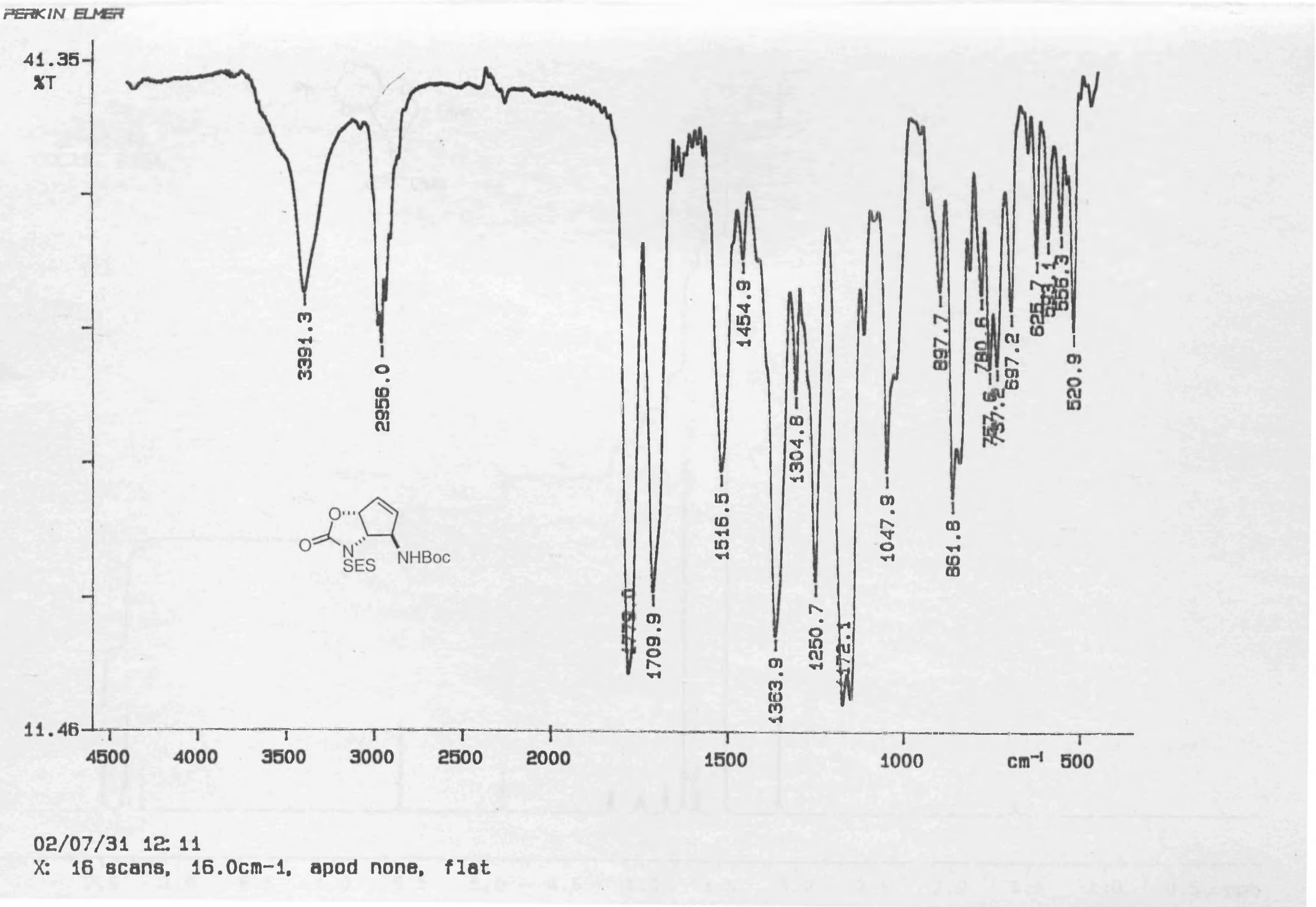




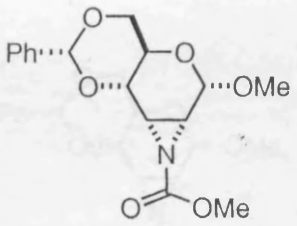
II-md-56
CDCl3, 298 K
COSY



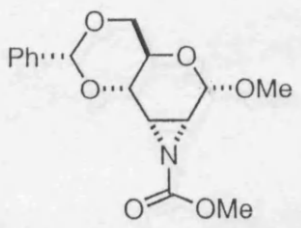



PERKIN ELMER
41.35
%T
11.46
3391.3
2956.0
1709.9
1516.5
1454.9
1363.9
1304.8
1250.7
1172.1
1047.9
897.7
861.8
780.6
757.6
737.2
697.2
625.7
556.3
520.9
4500
4000
3500
3000
2500
2000
1500
1000
cm-1
500
O
O
N
SES
NHBoc
02/07/31 12:11
X: 16 scans, 16.0cm-1, apod none, flat

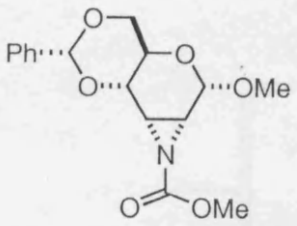
II-md-94
CDCl3, 298K

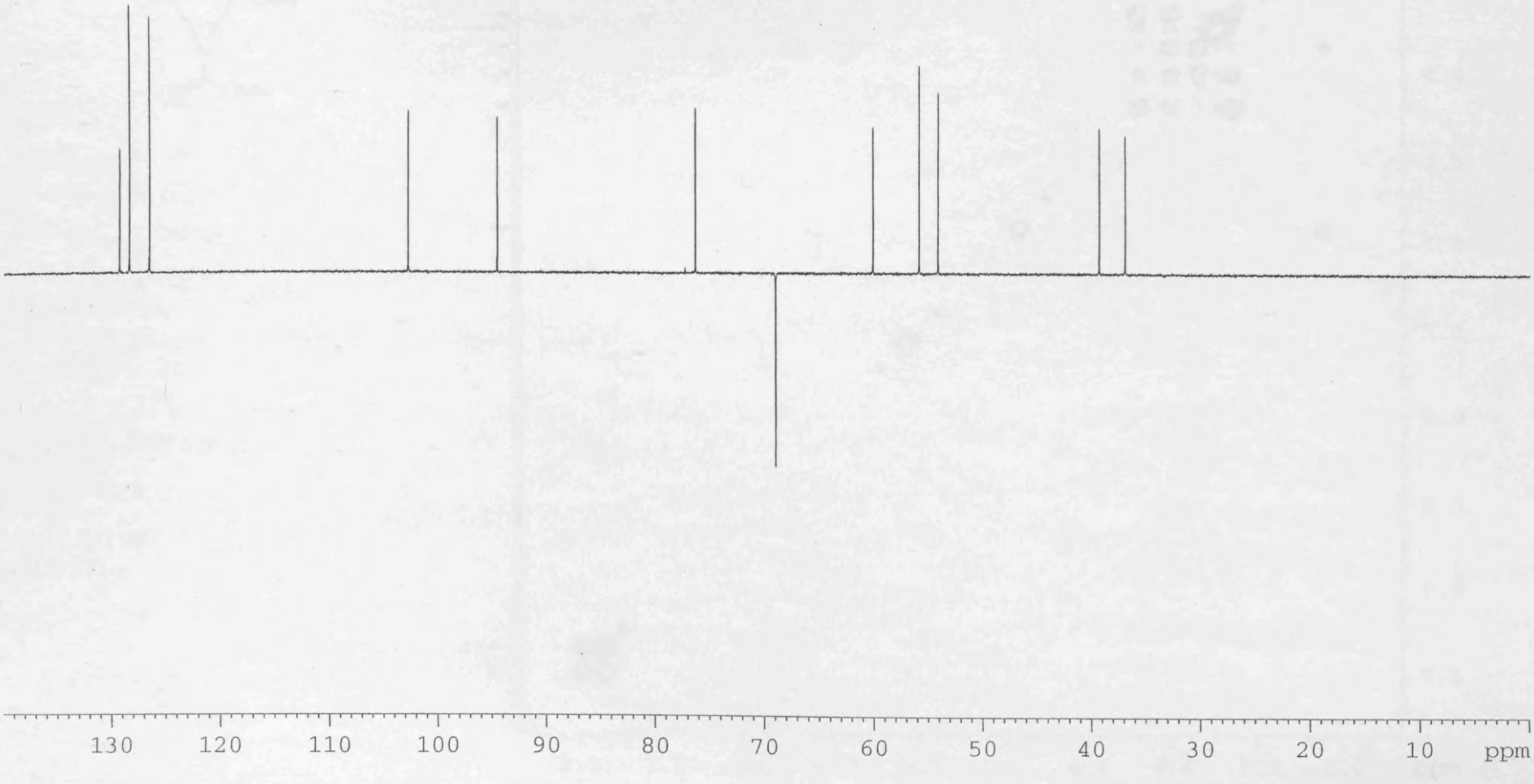


II-md-94
CDCl3, 298 K

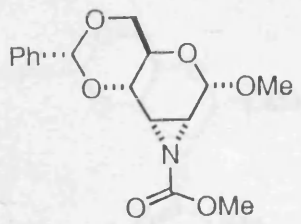


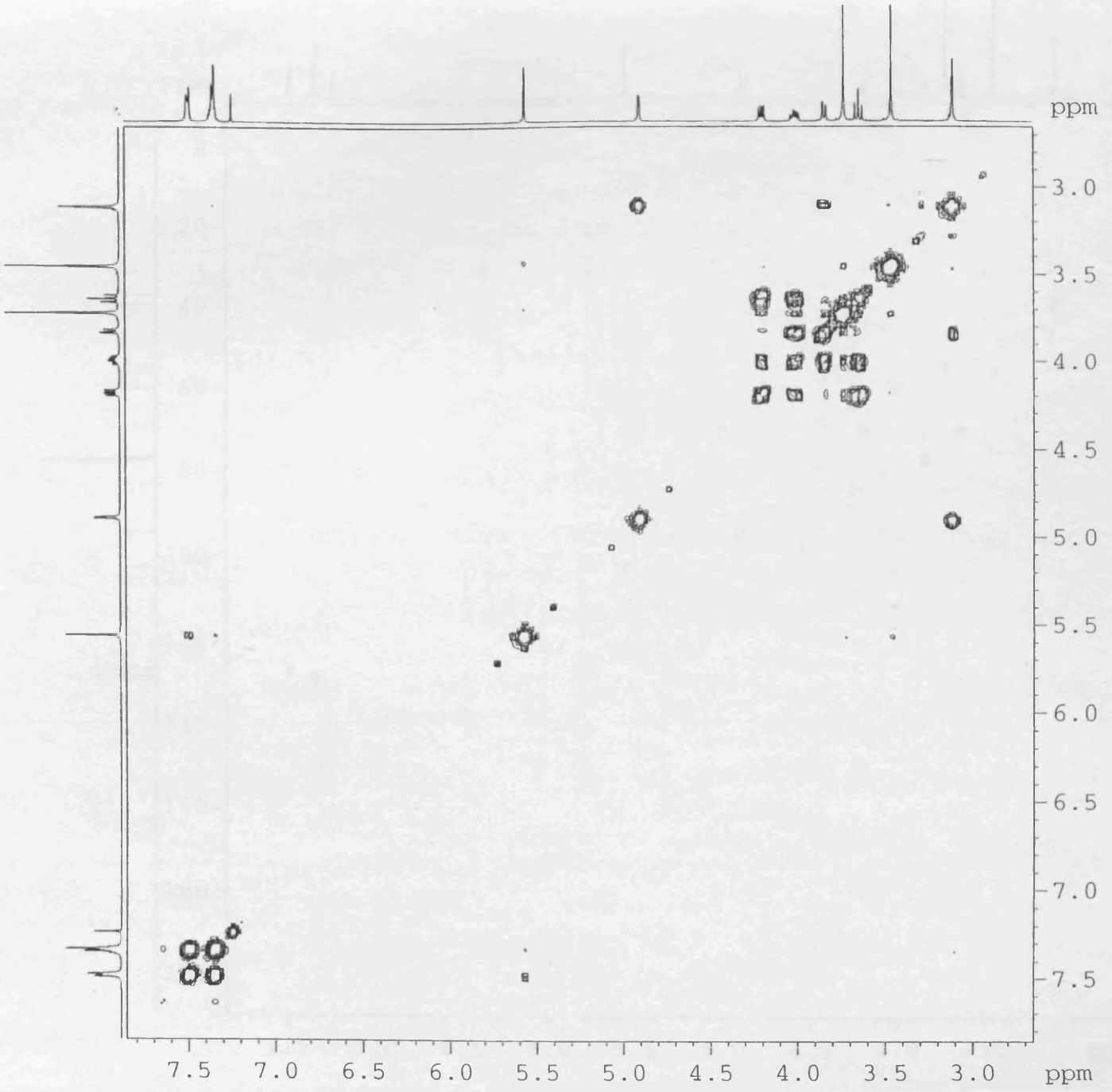
II-md-94
CDCl3, 298 K
DEPT



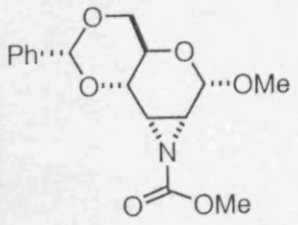


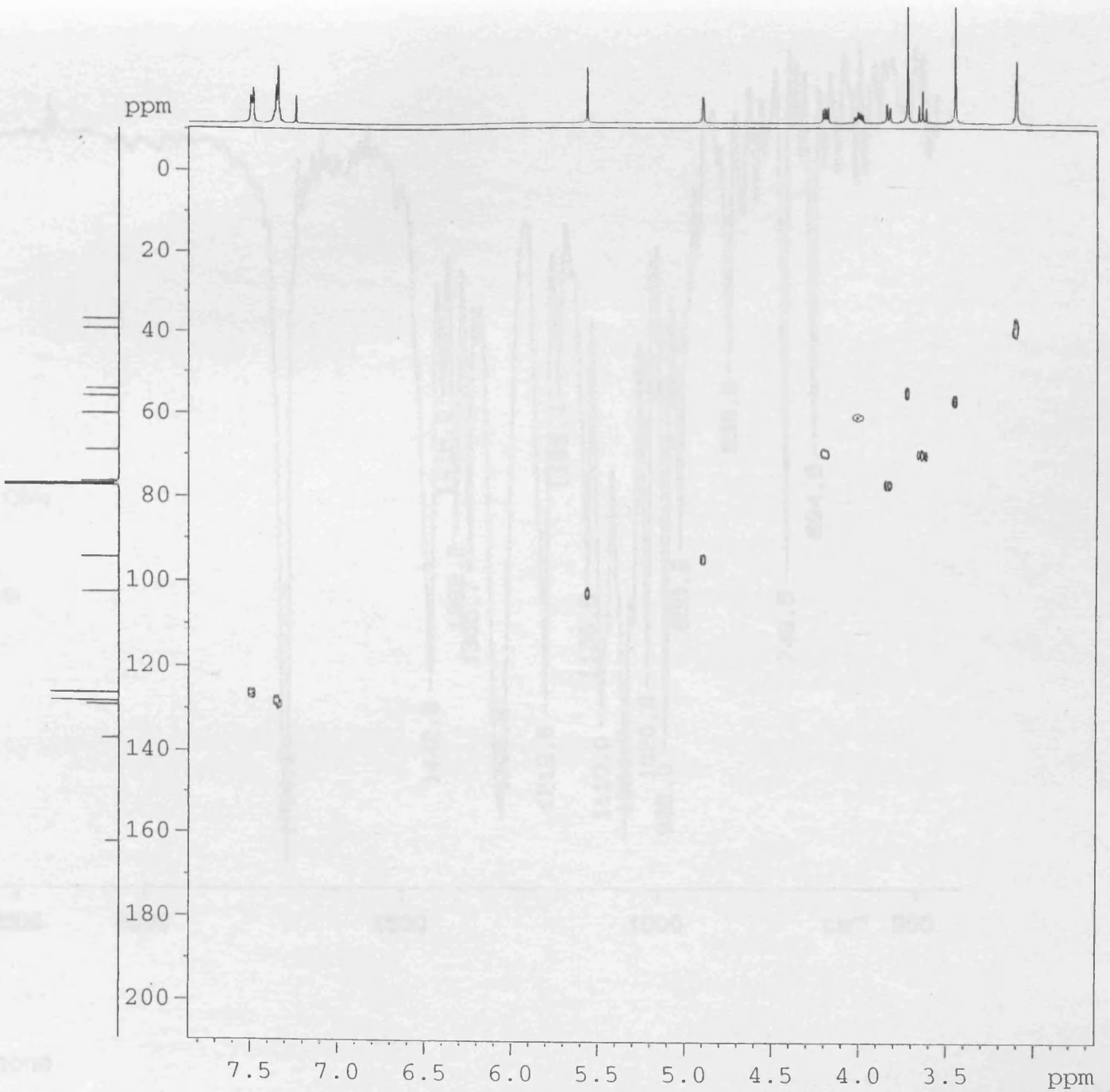
II-md-94
CDCl3, 298 K
COSY

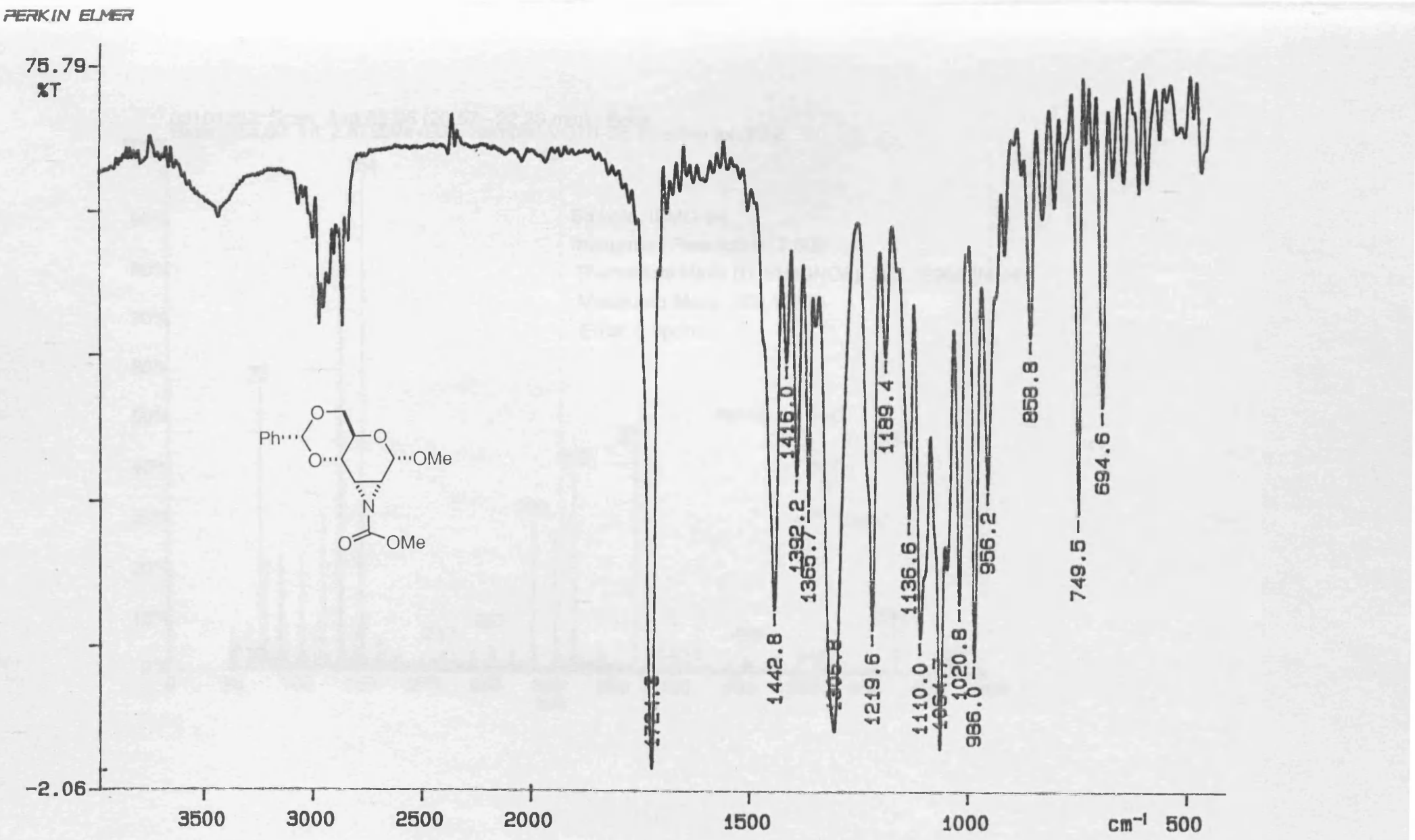




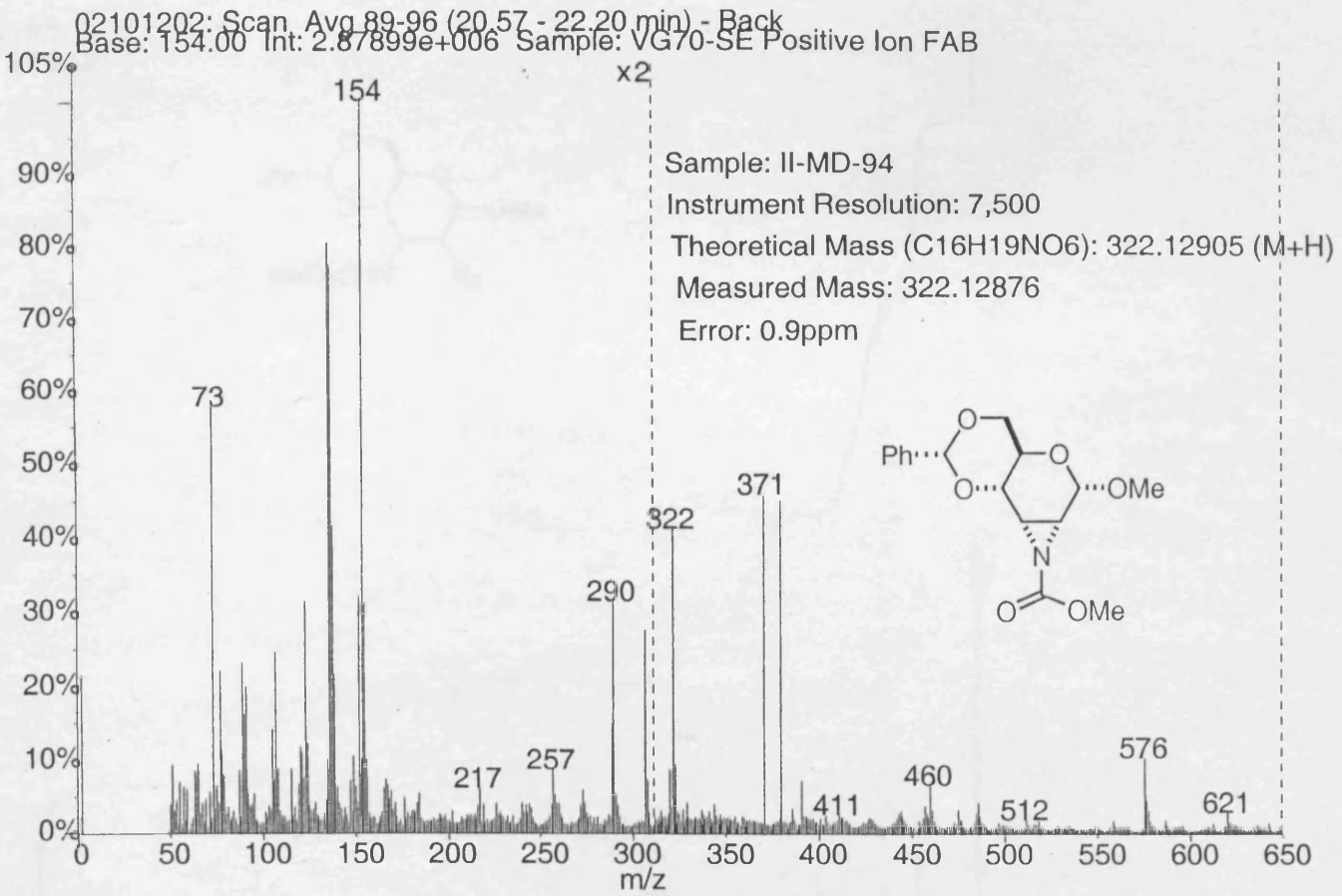
II-md-94
CDCl3, 298 K
HMQC



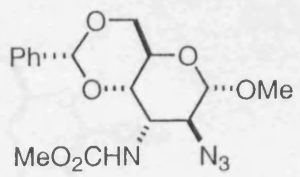




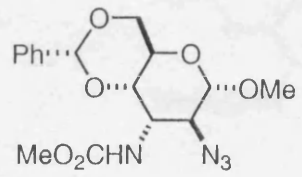
02/10/29 11:43
X: 64 scans, 16.0cm-1, apod none


02101202: Scan Avg 89-96 (20.57 - 22.20 min) - Back
Base: 154.00 Int: 2.87899e+006 Sample: VG70-SE Positive Ion FAB
105%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
154
x2
73
371
322
290
217
257
411
460
512
576
621
0
50
100
150
200
250
300
350
400
450
500
550
600
650
m/z
Sample: II-MD-94
Instrument Resolution: 7,500
Theoretical Mass (C16H19NO6): 322.12905 (M+H)
Measured Mass: 322.12876
Error: 0.9ppm
Ph
O
O
O
OMe
N
O
OMe

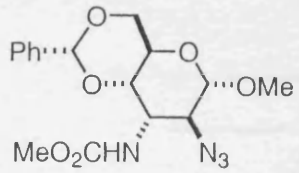
II-md-96
CDCl3, 298 K

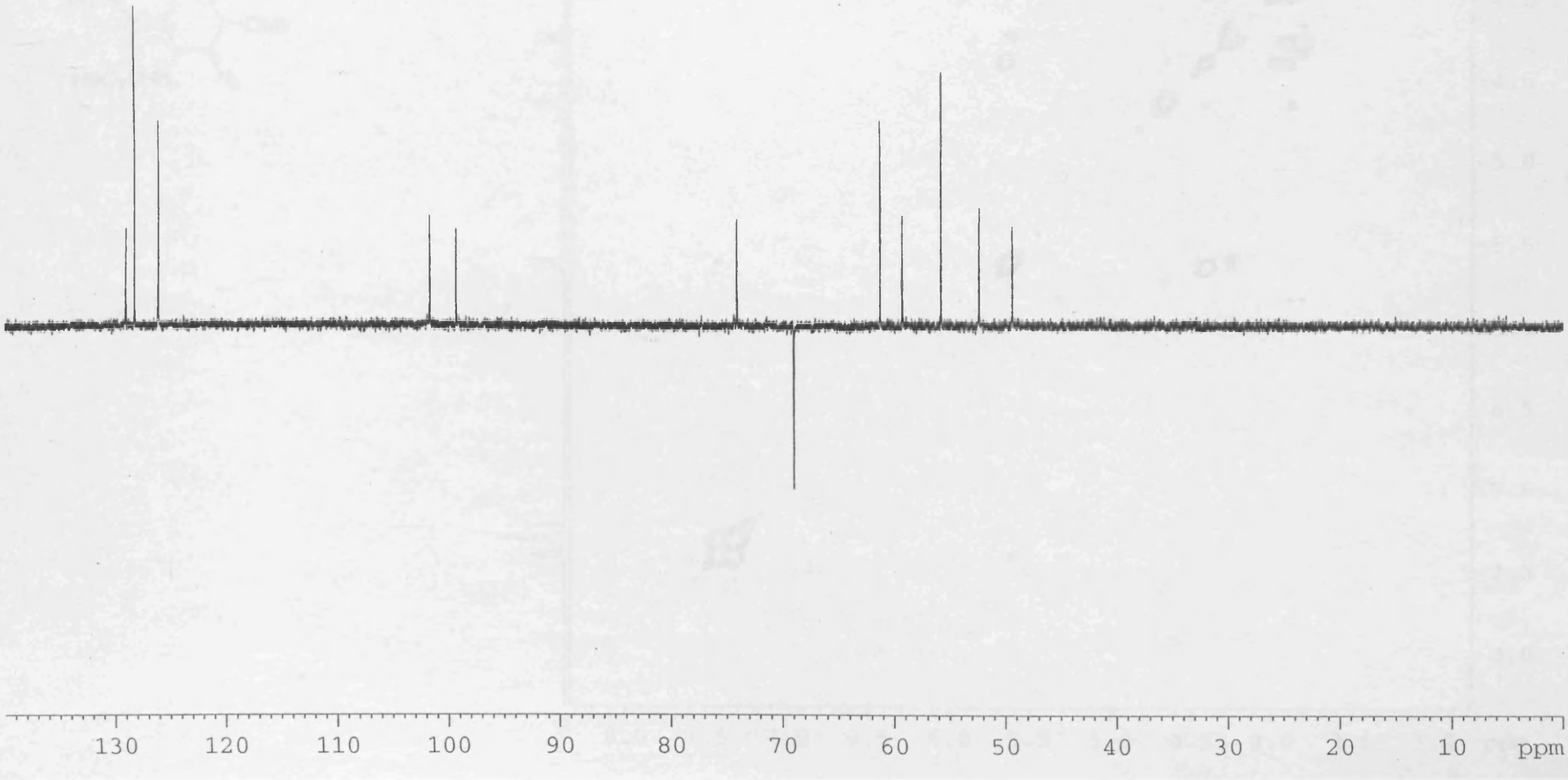


II-md-96
CDCl3, 298 K

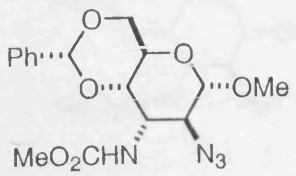


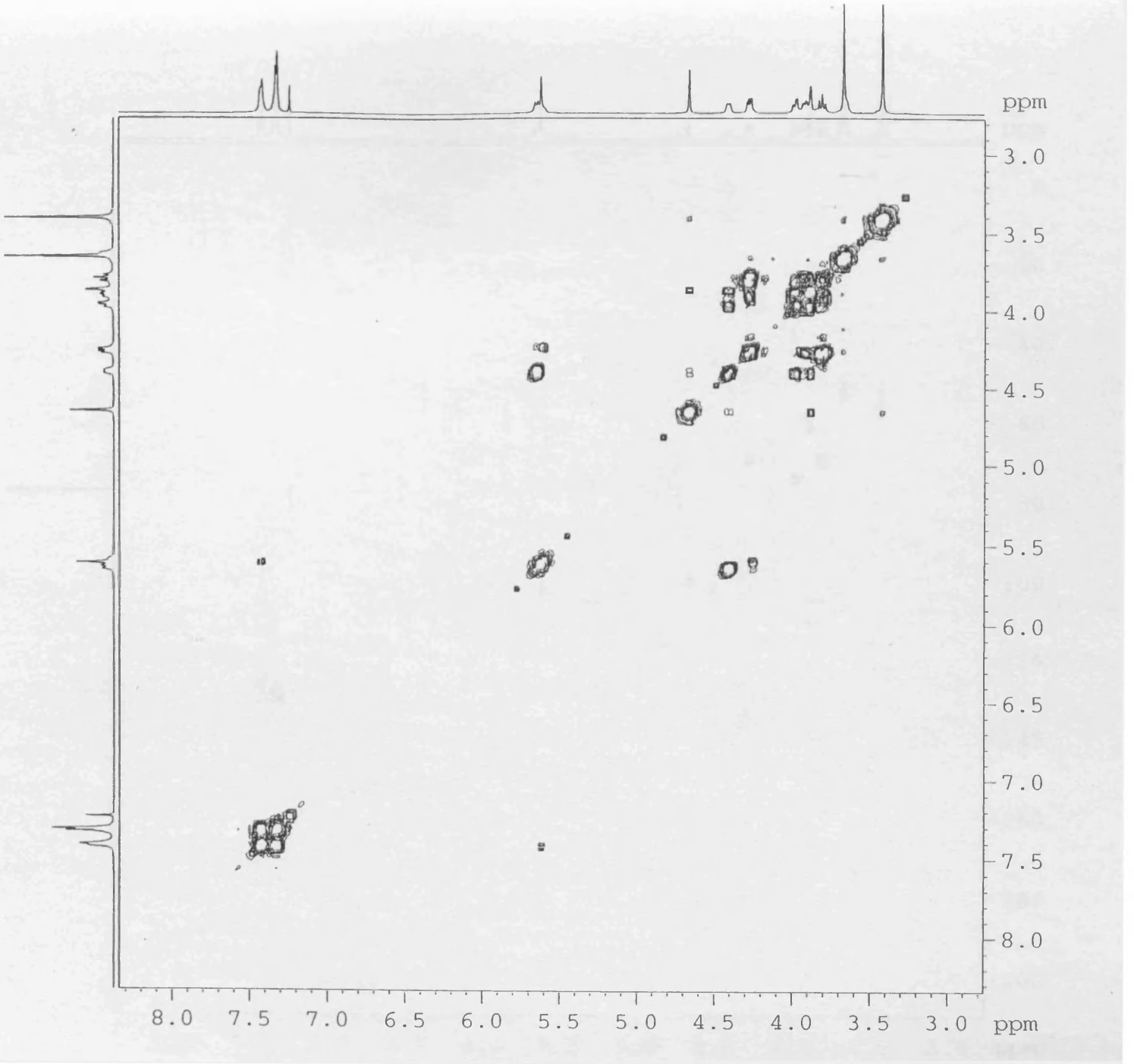
II-md-96
CDCl3, 298 K
DEPT



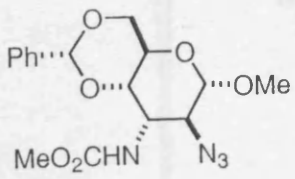


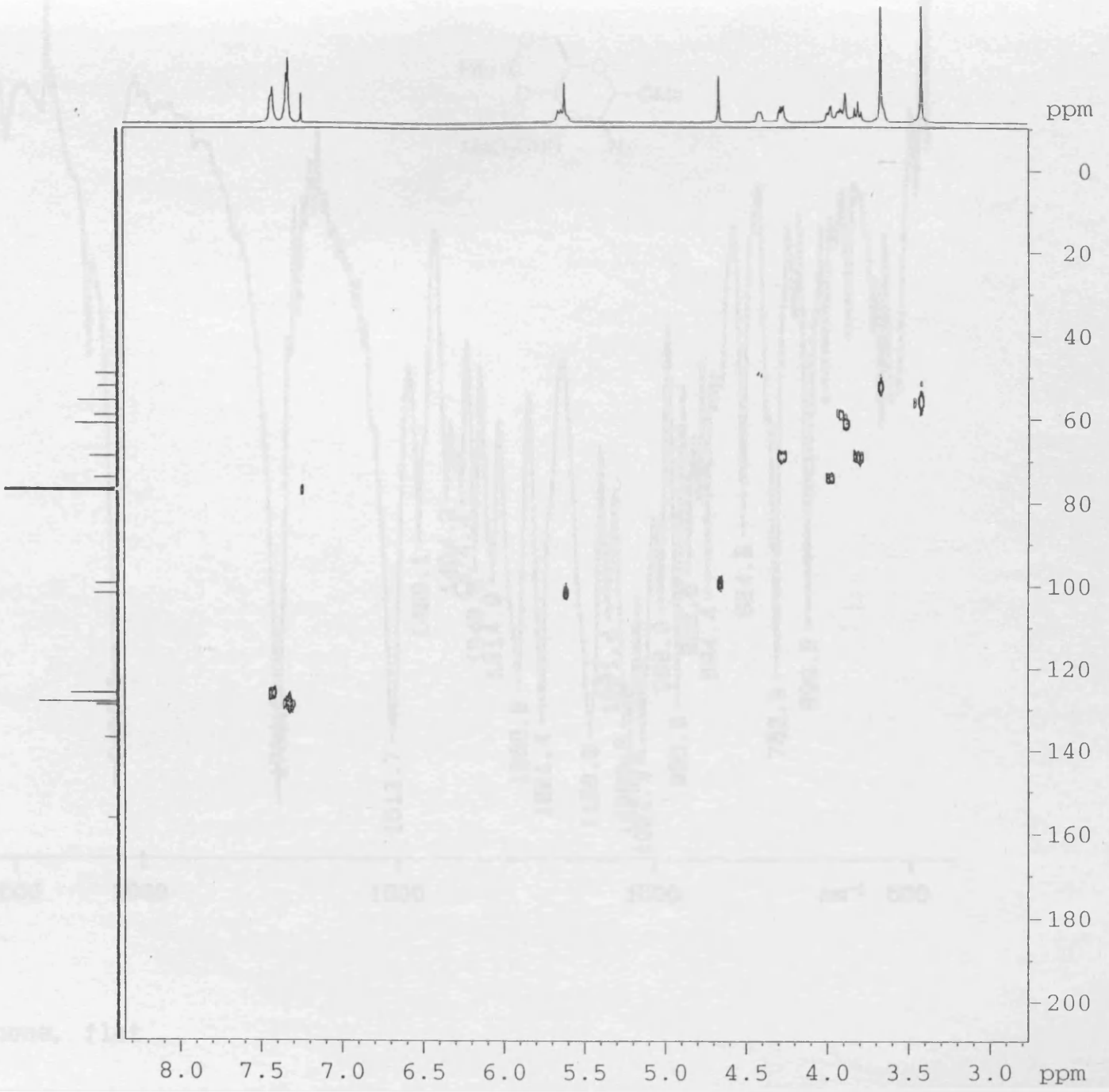
II-md-96
CDCl3, 298 K
COSY

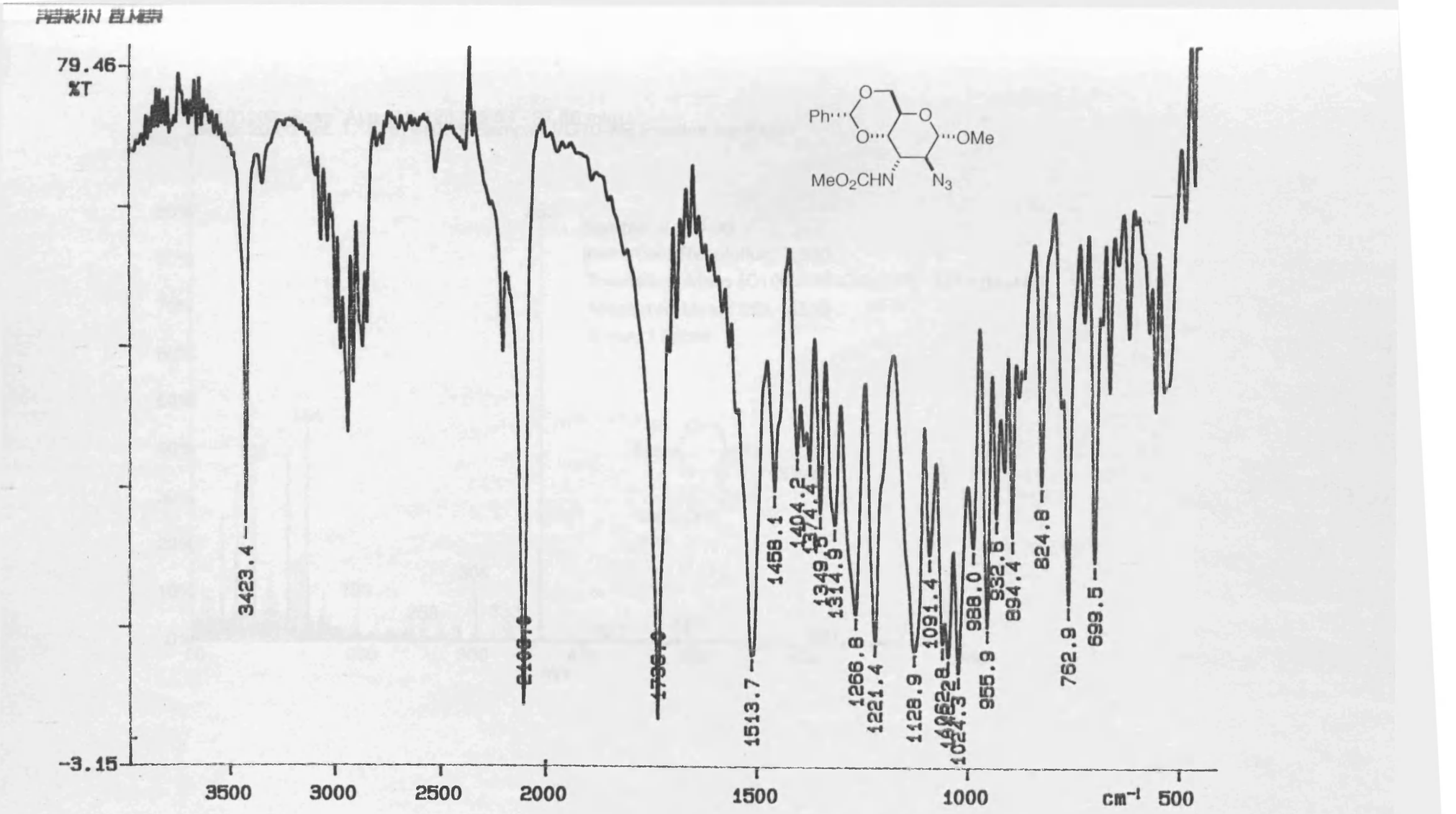




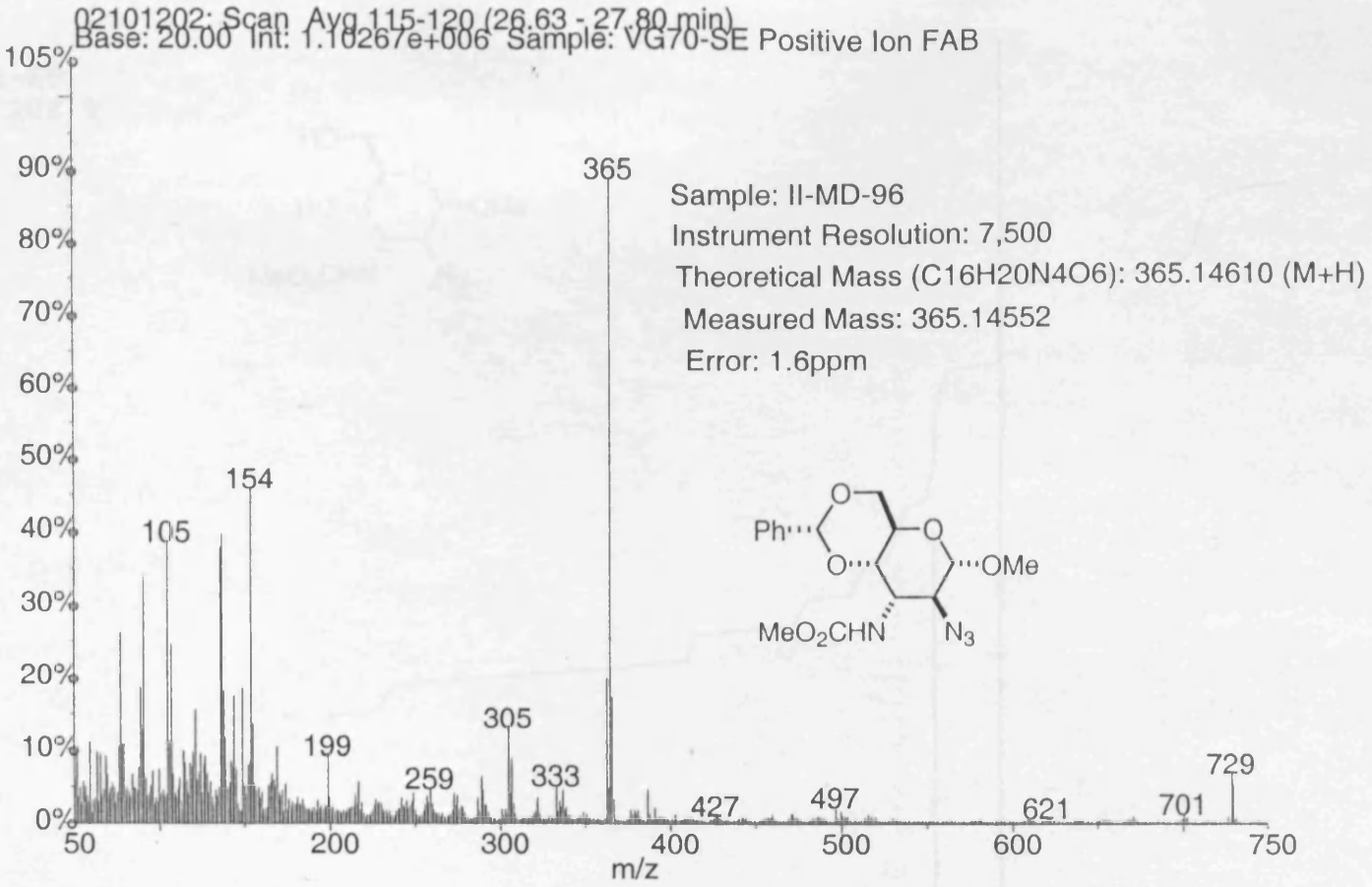
II-md-96
CDCl3, 298 K



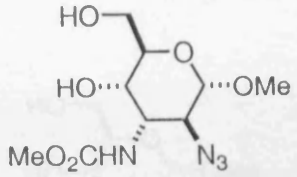




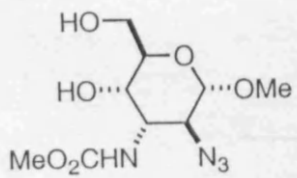
02/10/29 12:56
X: 64 scans, 16.0cm-1, apod none, flat


02101202: Scan Avg 115-120 (26.63 - 27.80 min)
Base: 20.00 Int: 1.10267e+006 Sample: VG70-SE Positive Ion FAB
105%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
365
154
105
199
305
259
333
427
497
621
701
729
50
200
300
400
500
600
750
m/z
Sample: II-MD-96
Instrument Resolution: 7,500
Theoretical Mass (C16H20N4O6): 365.14610 (M+H)
Measured Mass: 365.14552
Error: 1.6ppm
Ph
O
O
O
OMe
MeO2CHN
N3

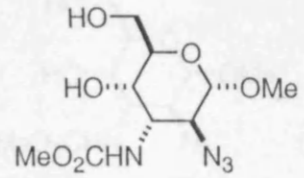
II-md-69
CDCl3, 298 K

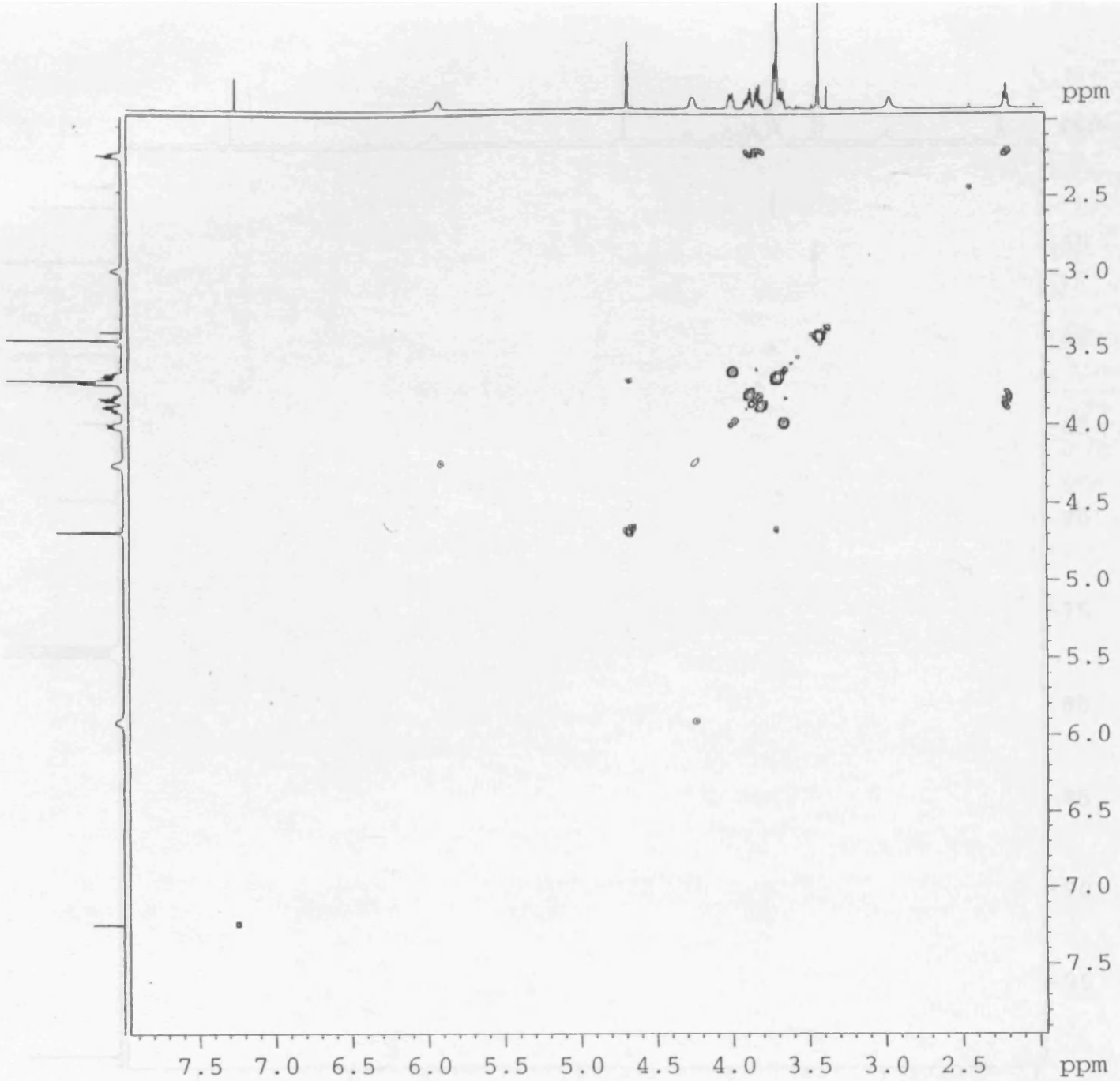


II-md-69
CDCl3, 298 K

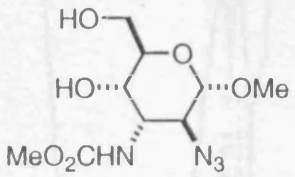


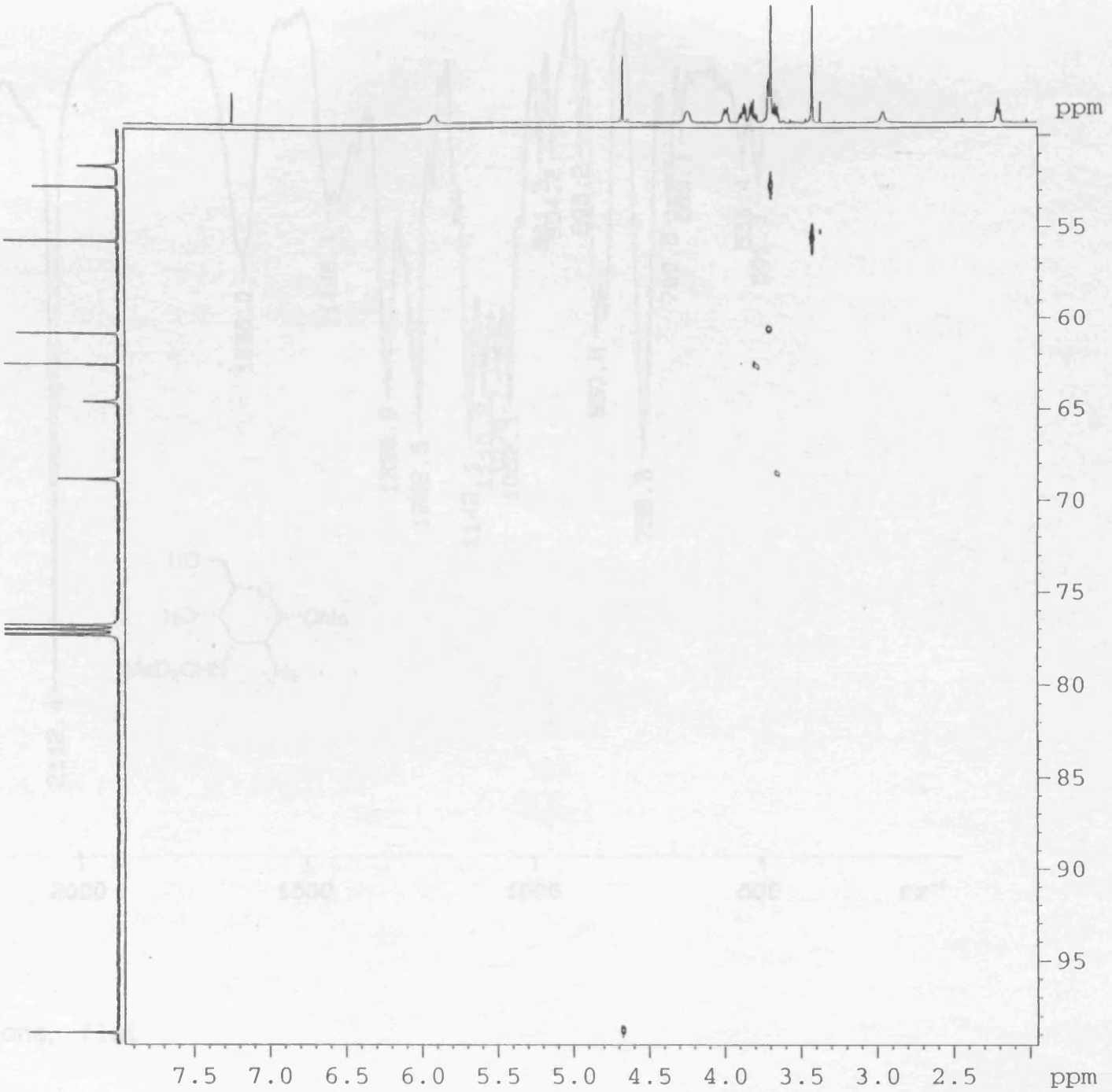
II-md-69
CDCl3, 298 K
COSY

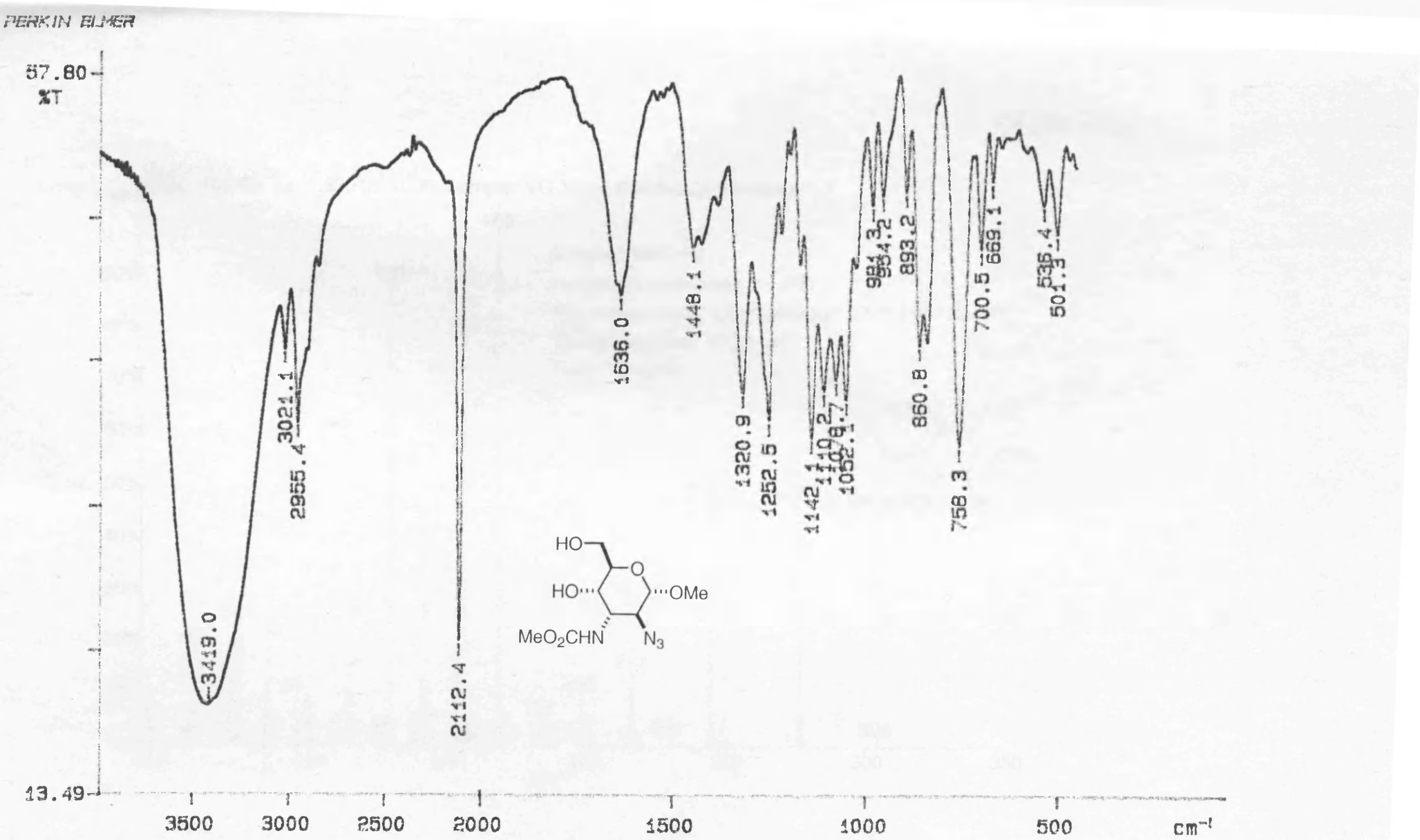


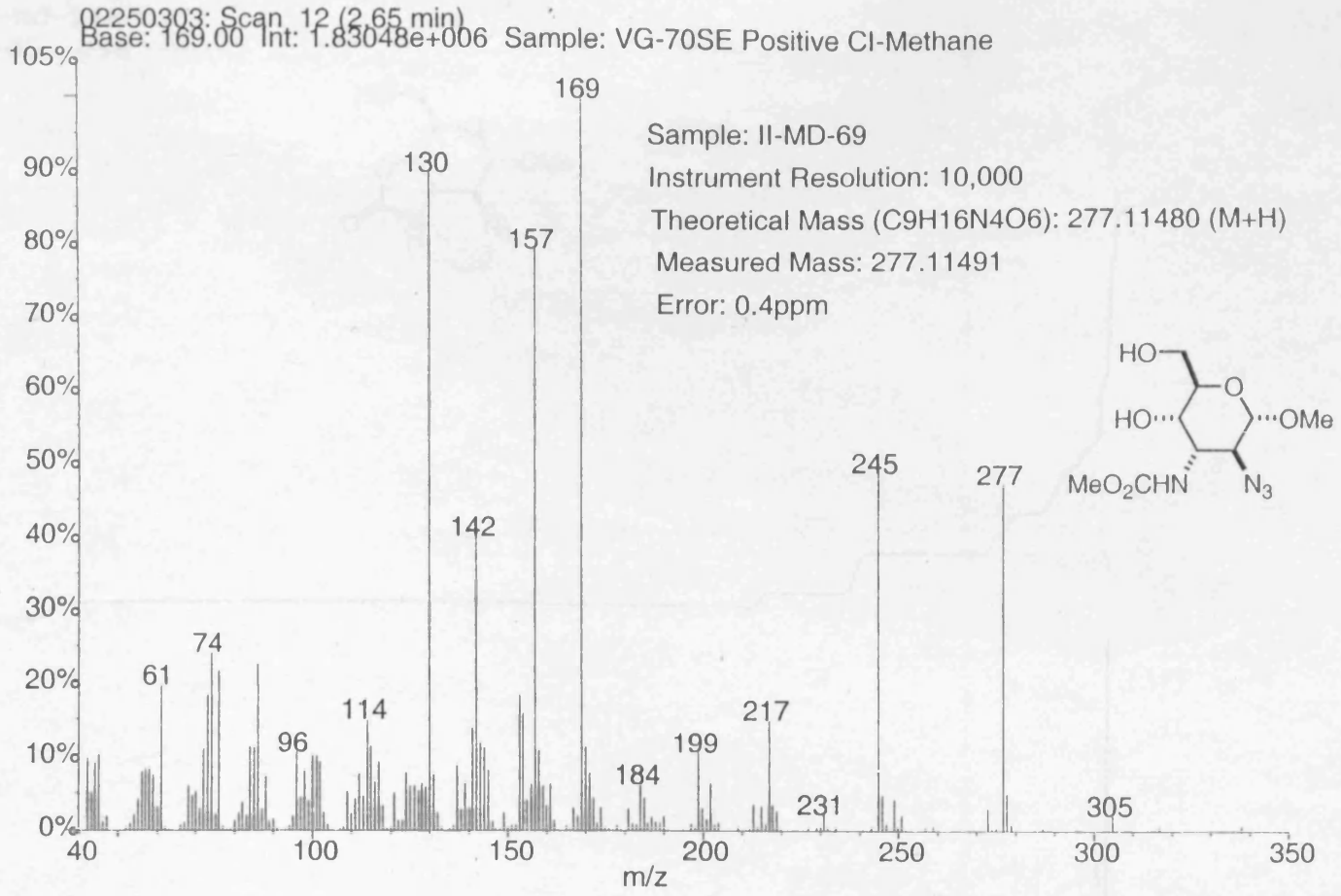


II-md-69
CDCl3, 298 K
HMQC

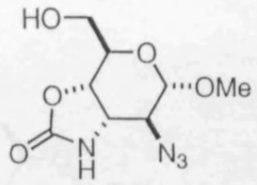


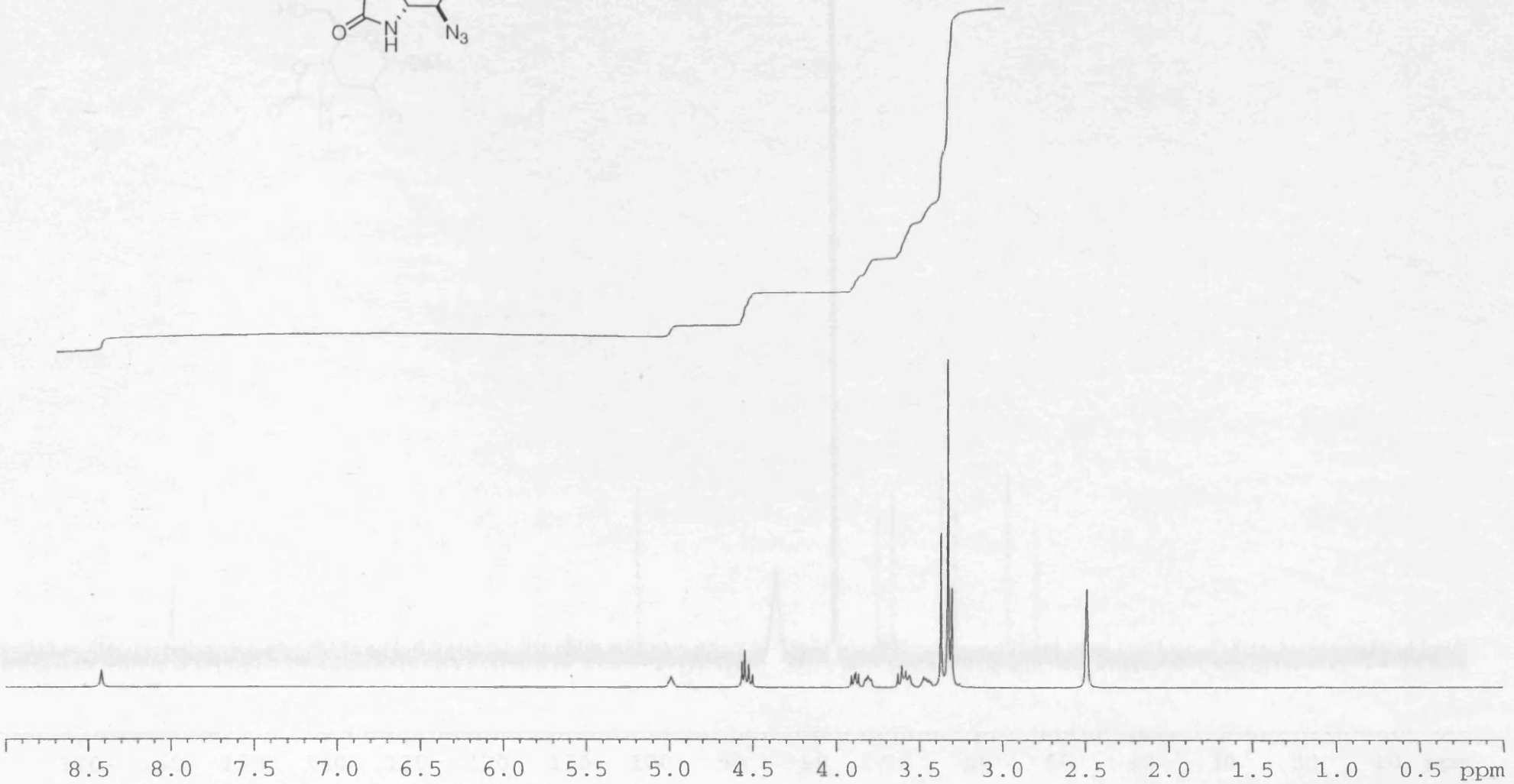



PERKIN ELMER
57.80
%T
13.49
3419.0
3021.1
2955.4
2112.4
1636.0
1448.1
1320.9
1252.5
1142.1
1110.2
1052.1
1018.7
984.3
954.2
893.2
860.8
758.3
700.5
669.1
536.4
501.9
HO
HO
O
OMe
MeO2CHN
N3
3500
3000
2500
2000
1500
1000
500
cm-1
03/01/16 11:15
X: 16 scans, 16.0cm-1, apod none, flat

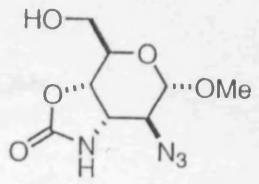

02250303: Scan 12 (2.65 min)
Base: 169.00 Int: 1.83048e+006 Sample: VG-70SE Positive CI-Methane
Sample: II-MD-69
Instrument Resolution: 10,000
Theoretical Mass (C9H16N4O6): 277.11480 (M+H)
Measured Mass: 277.11491
Error: 0.4ppm
HO
O
HO
OMe
MeO2CHN
N3
105%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
169
130
157
142
74
61
96
114
199
184
217
231
245
277
305
40
100
150
200
250
300
350
m/z

II-md-146
MSO-d6, 298

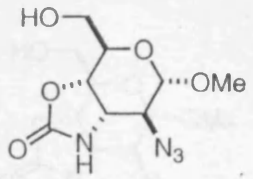


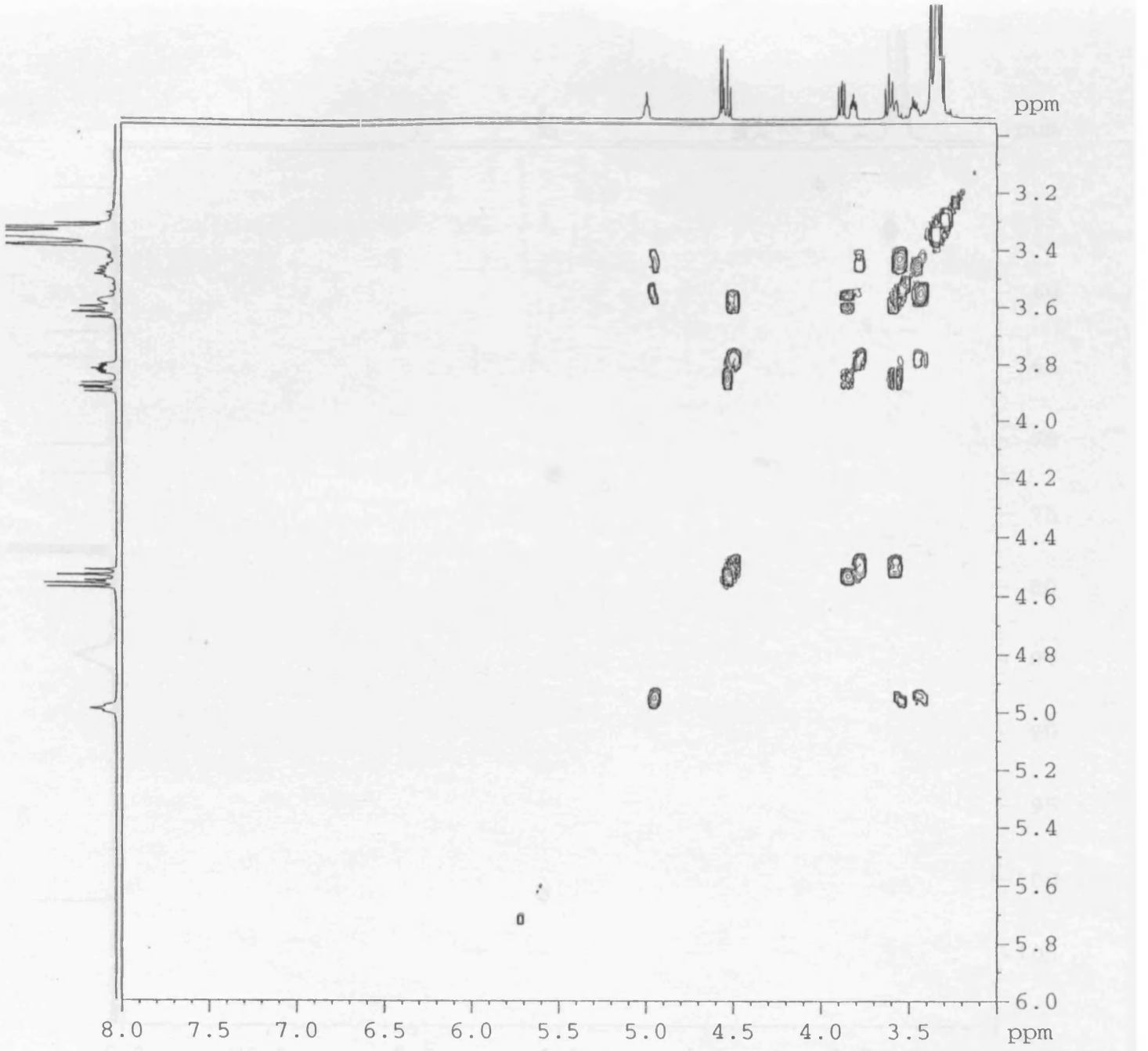


II-md-146
DMSO-d6, 298 K

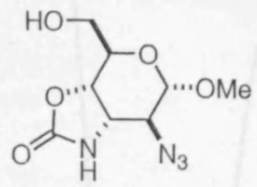


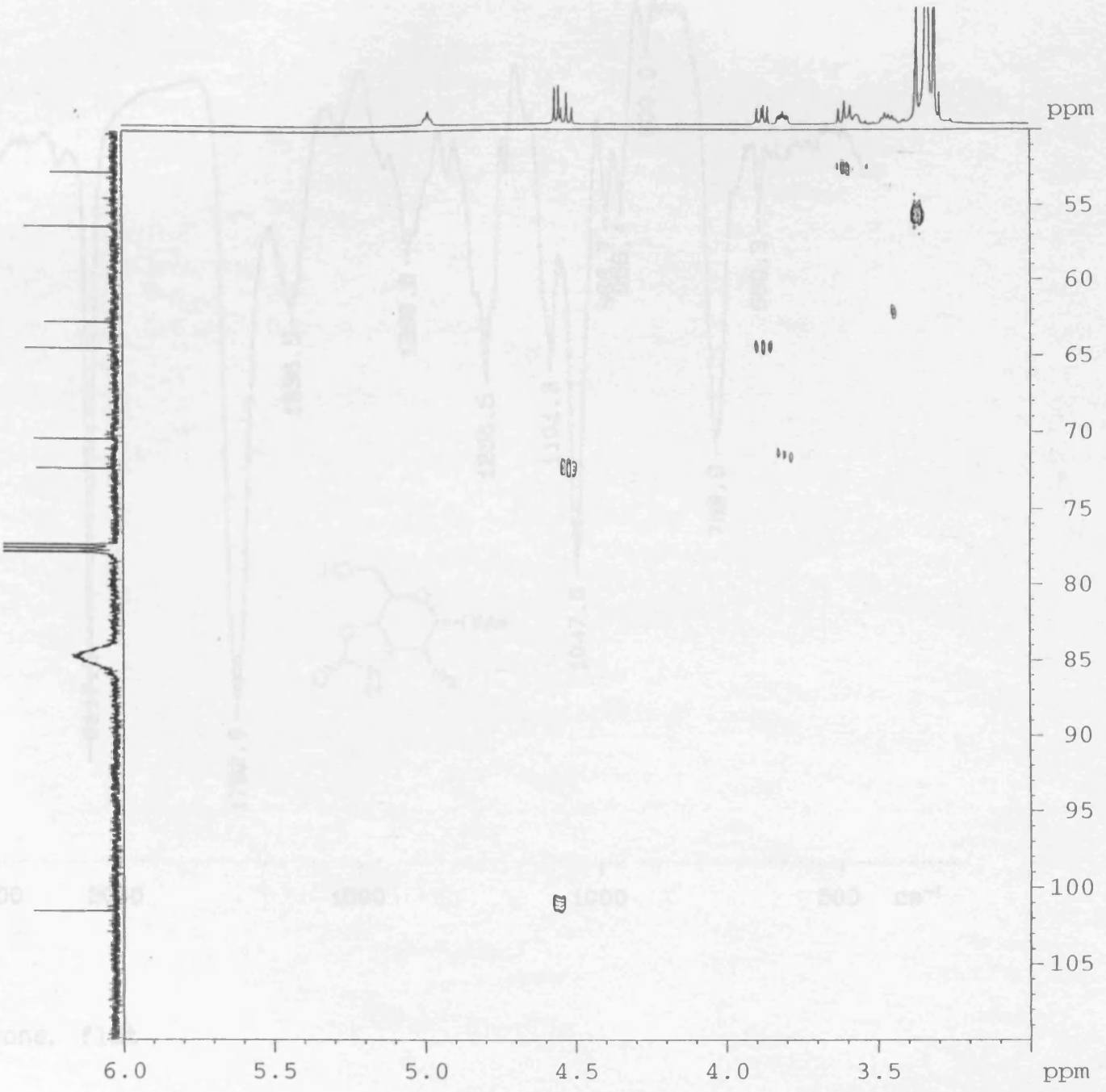
II-md-146
DMSO-d6, 298 K
COSY

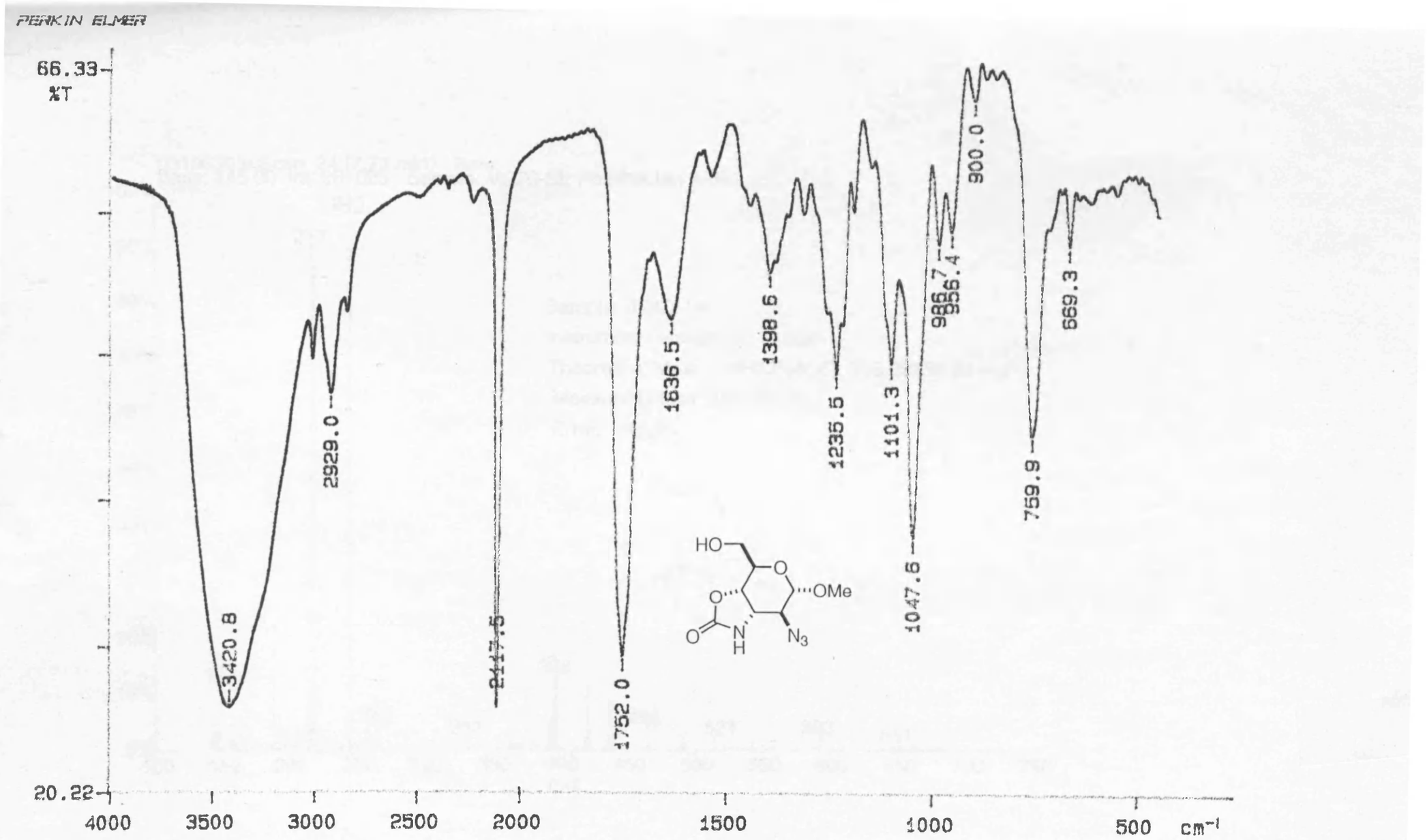




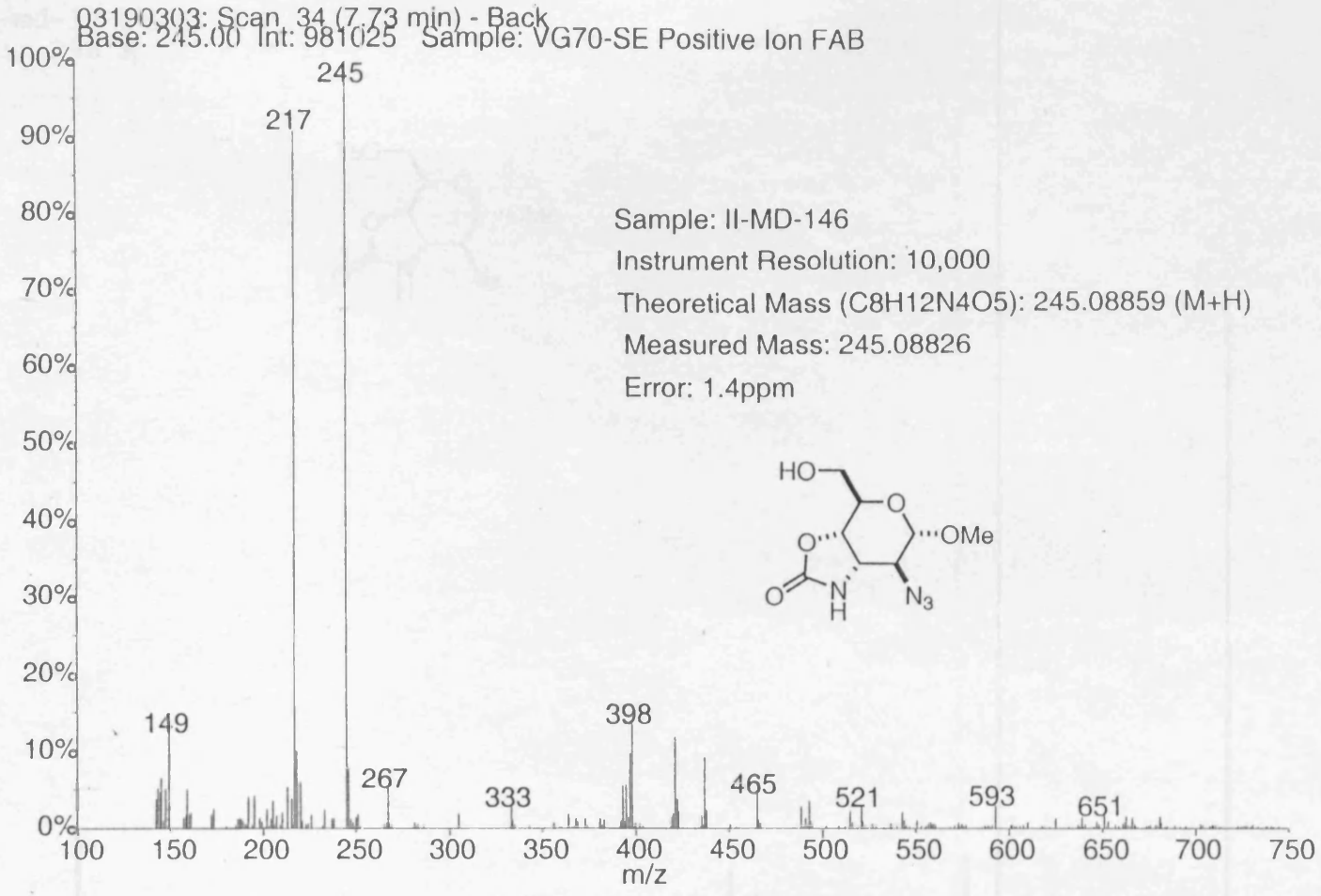
II-md-146
DMSO-d6, 298 K
HMQC



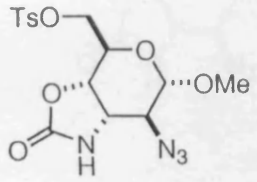




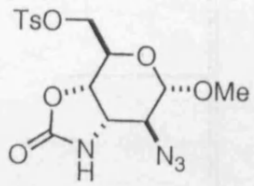
03/01/16 11:09
X: 16 scans, 16.0cm-1, apod none, flat


03190303: Scan 34 (7.73 min) - Back
Base: 245.00 Int: 981025 Sample: VG70-SE Positive Ion FAB
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
245
217
149
267
333
398
465
521
593
651
100
150
200
250
300
350
400
450
500
550
600
650
700
750
m/z
Sample: II-MD-146
Instrument Resolution: 10,000
Theoretical Mass (C8H12N4O5): 245.08859 (M+H)
Measured Mass: 245.08826
Error: 1.4ppm
HO
O
OMe
O
O
N
H
N3

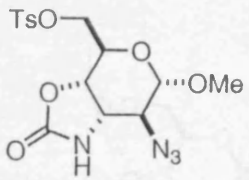
II-md-97
CDCl3, 298 K

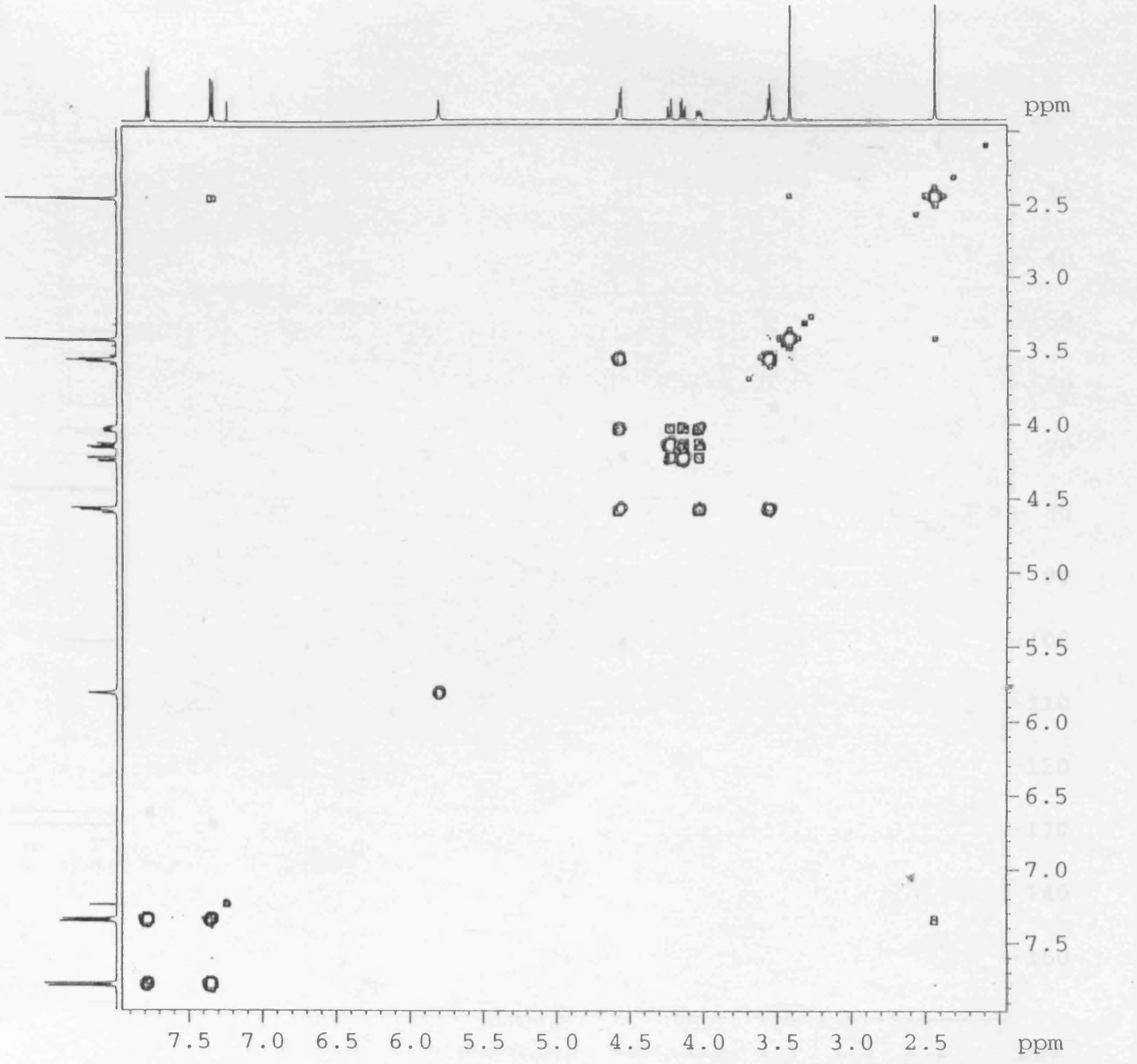


II-md-97
CDCl3, 298 K

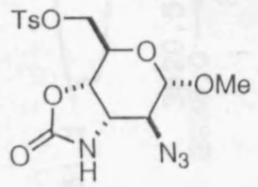


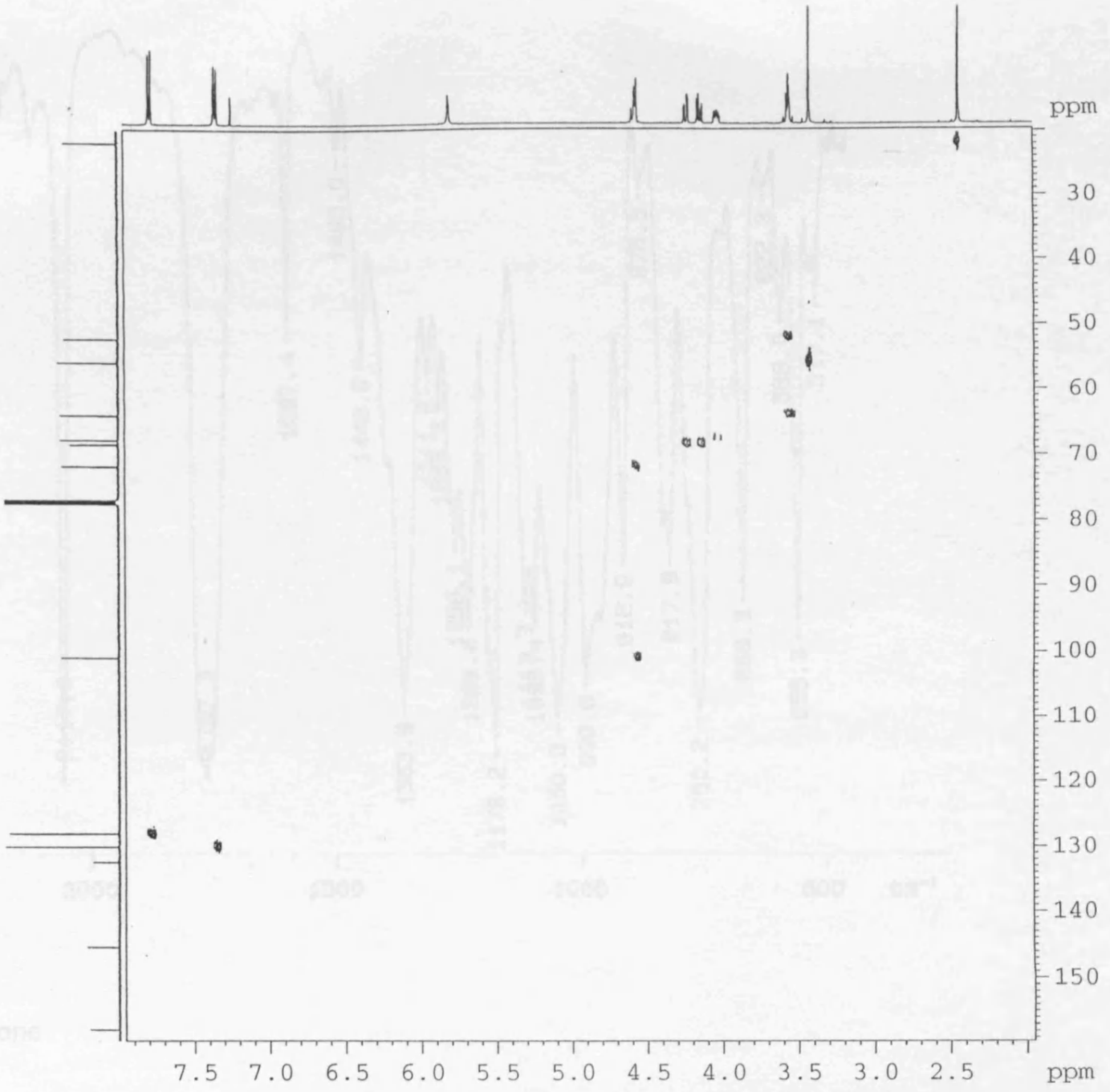
II-md-97
CDCl3, 298 K
COSY

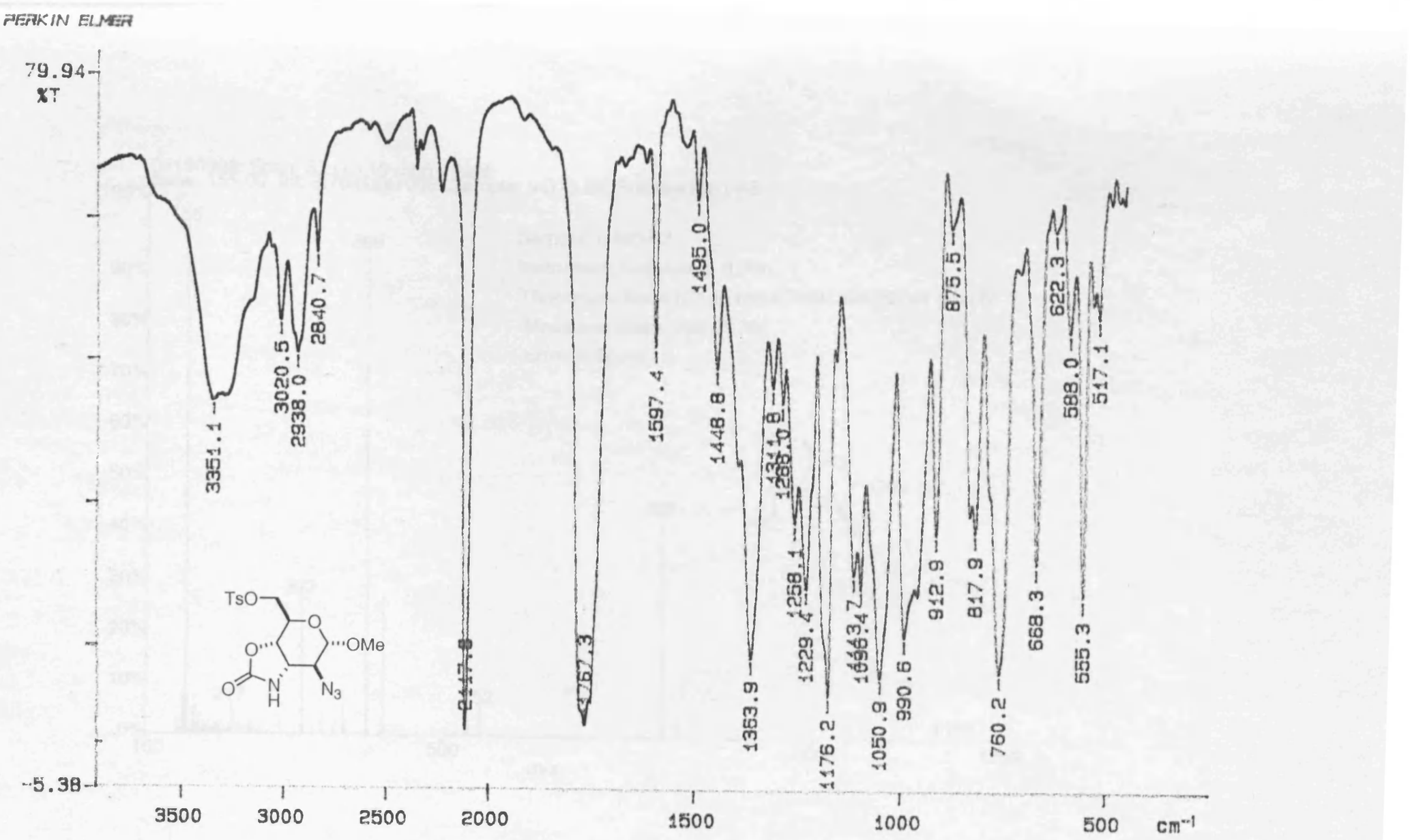




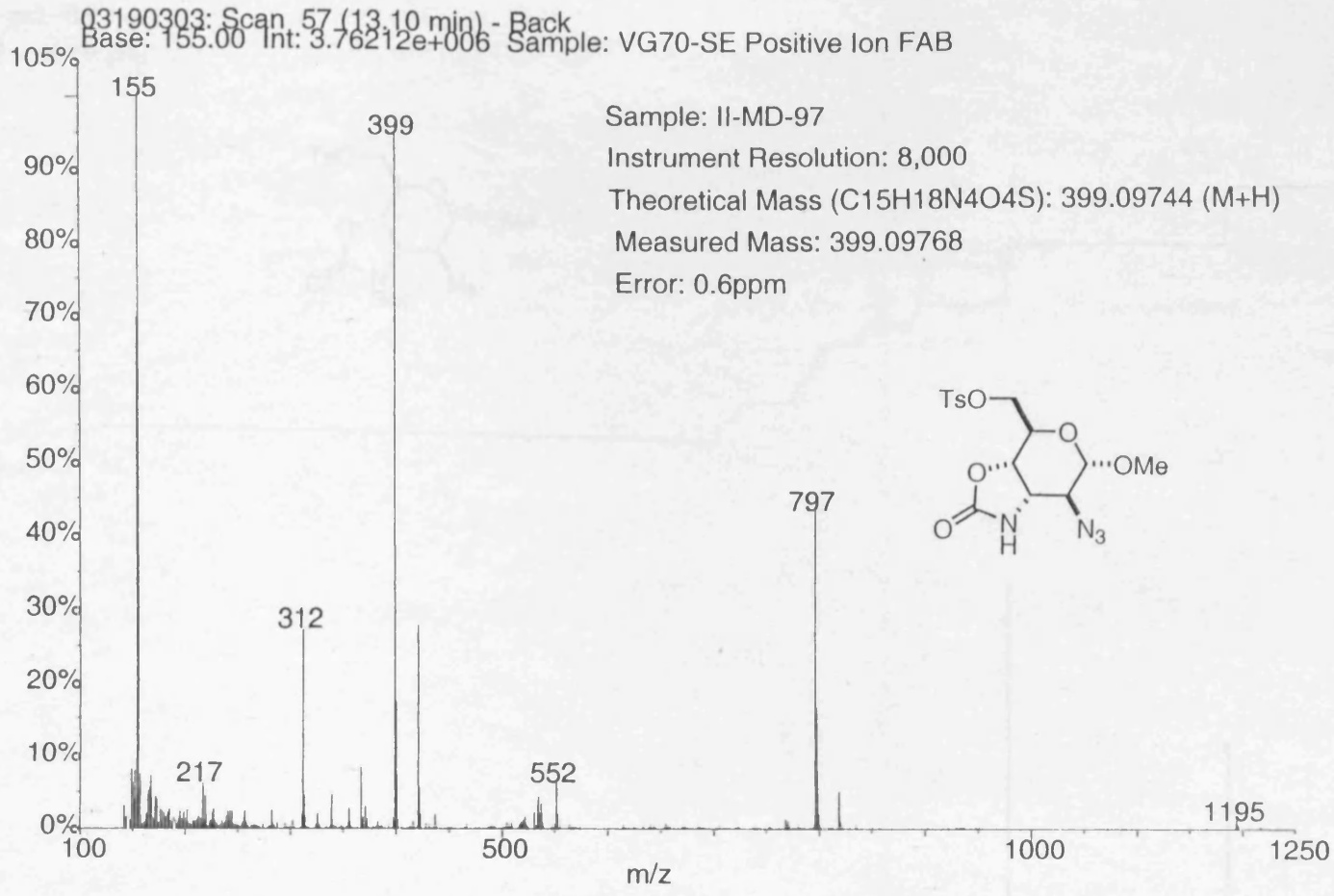
II-md-97
CDCl3, 298 K
HMQC



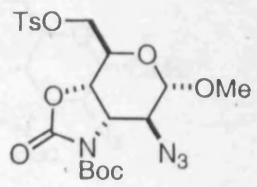




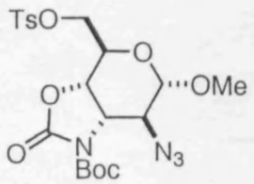
03/01/16 11:03
X: 16 scans, 16.0cm-1, apod none


03190303: Scan 57 (13.10 min) - Back
Base: 155.00 Int: 3.76212e+006 Sample: VG70-SE Positive Ion FAB
105%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
155
399
312
217
552
797
1195
100
500
1000
1250
m/z
Sample: II-MD-97
Instrument Resolution: 8,000
Theoretical Mass (C15H18N4O4S): 399.09744 (M+H)
Measured Mass: 399.09768
Error: 0.6ppm
TsO
O
OMe
O
O
N
H
N3

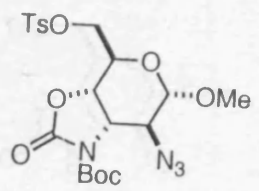
II-md-89
CDCl3, 298 K

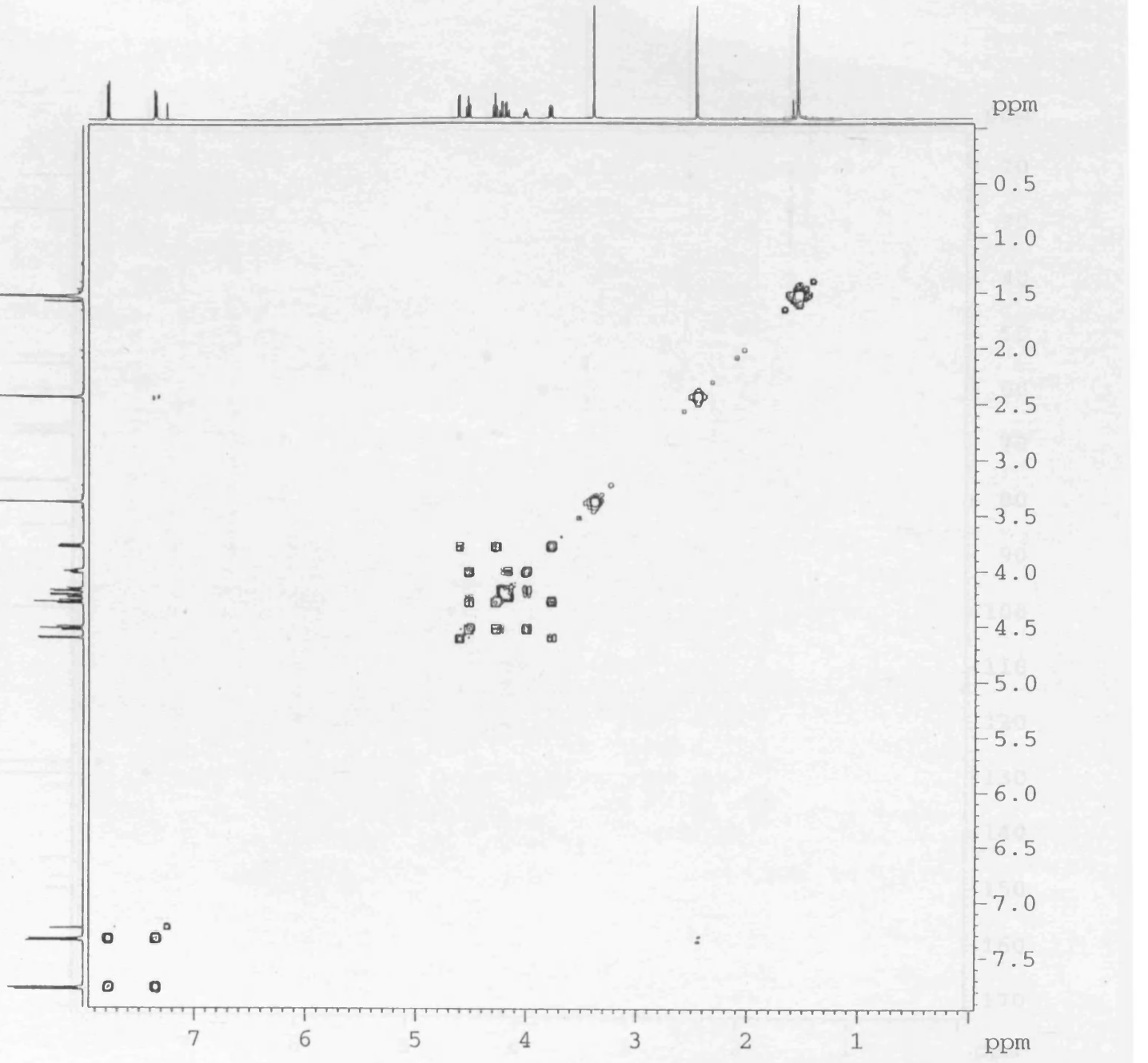


II-md-89
CDCl3, 298 K

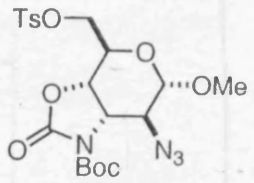


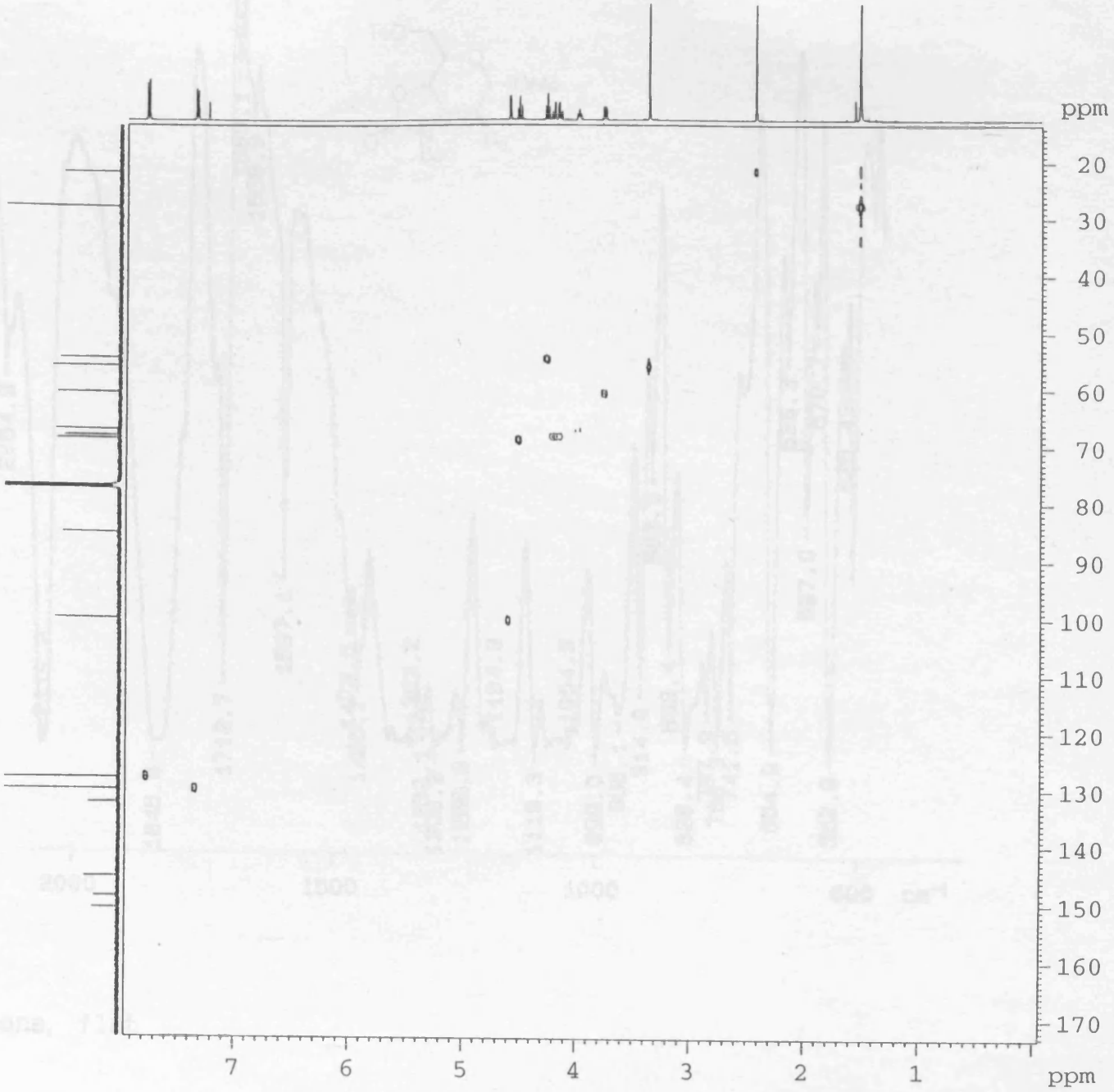
II-md-89
CDCl3, 298 K
COSY

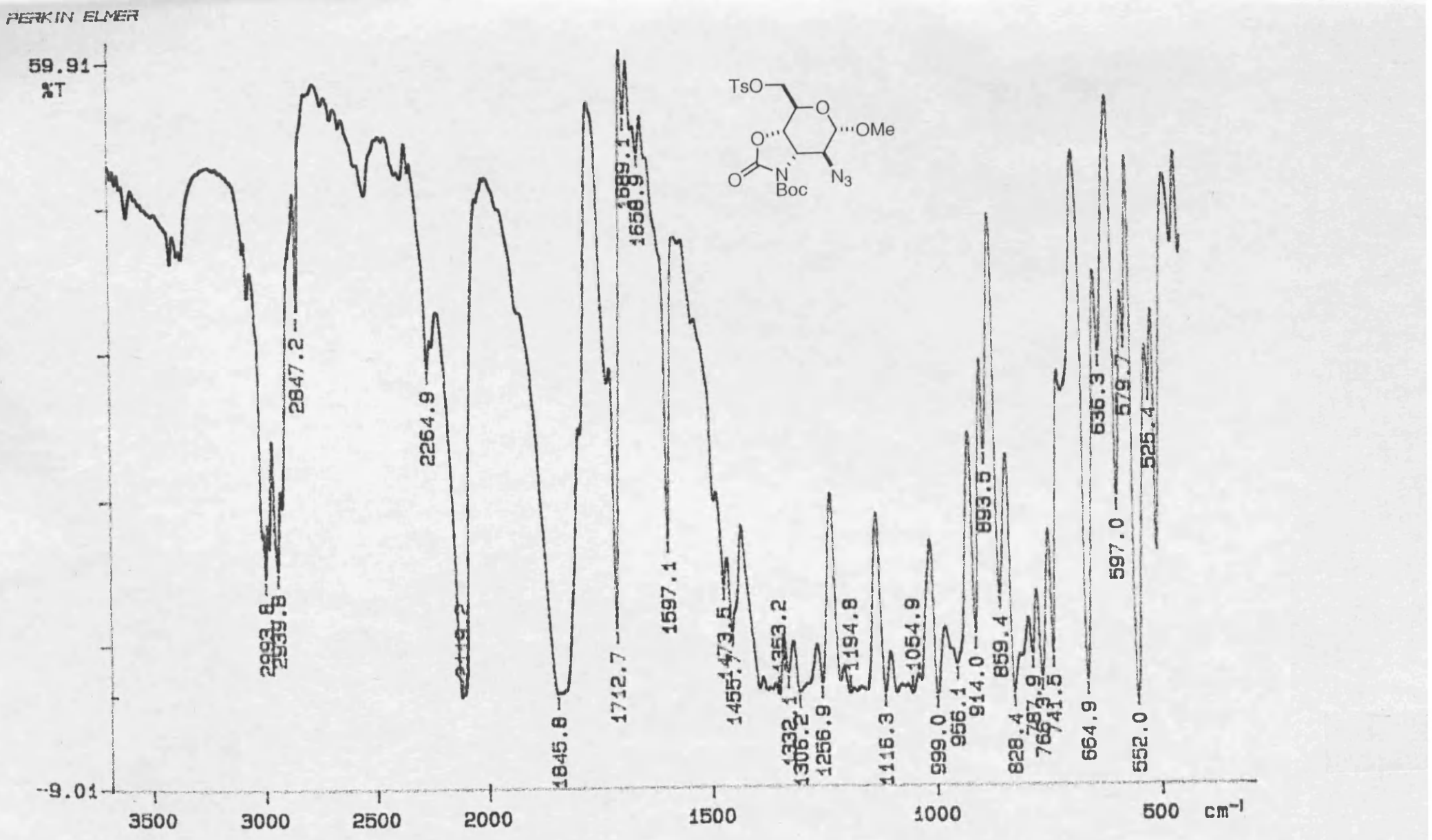




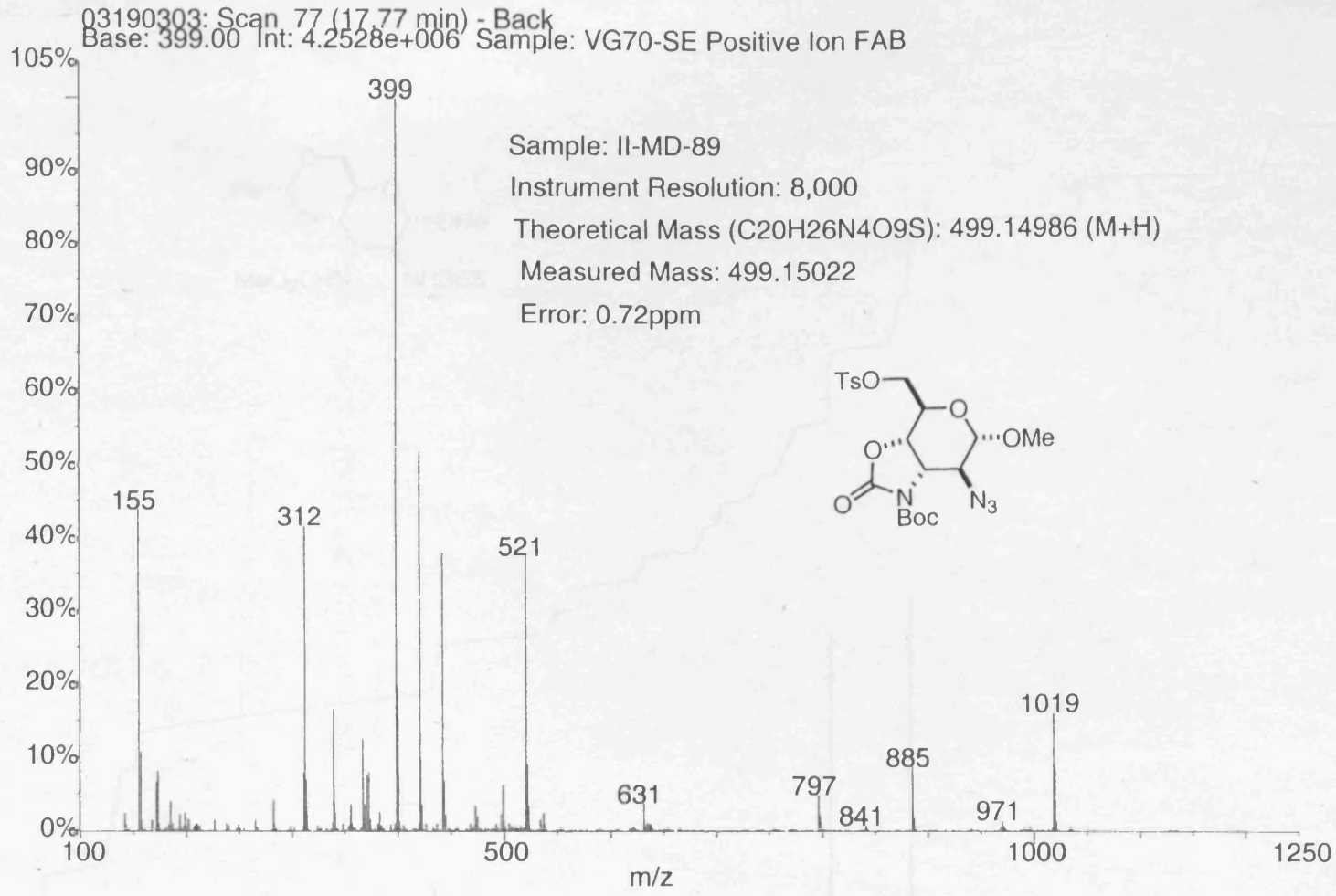
II-md-89
CDCl3, 298 K
HMQC



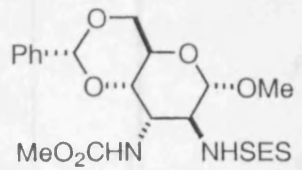




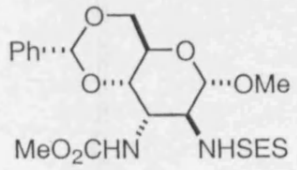
03/01/15 17:58
X: 16 scans, 16.0cm-1, apod none, flat


03190303: Scan 77 (17.77 min) - Back
Base: 399.00 Int: 4.2528e+006 Sample: VG70-SE Positive Ion FAB
105%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
399
155
312
521
631
797
841
885
971
1019
100
500
1000
1250
m/z
Sample: II-MD-89
Instrument Resolution: 8,000
Theoretical Mass (C20H26N4O9S): 499.14986 (M+H)
Measured Mass: 499.15022
Error: 0.72ppm
TsO
O
OMe
O
N
Boc
N3

II-md-149
toluene, 363 K

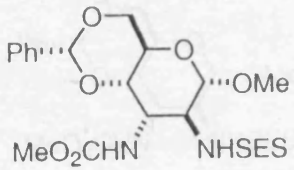


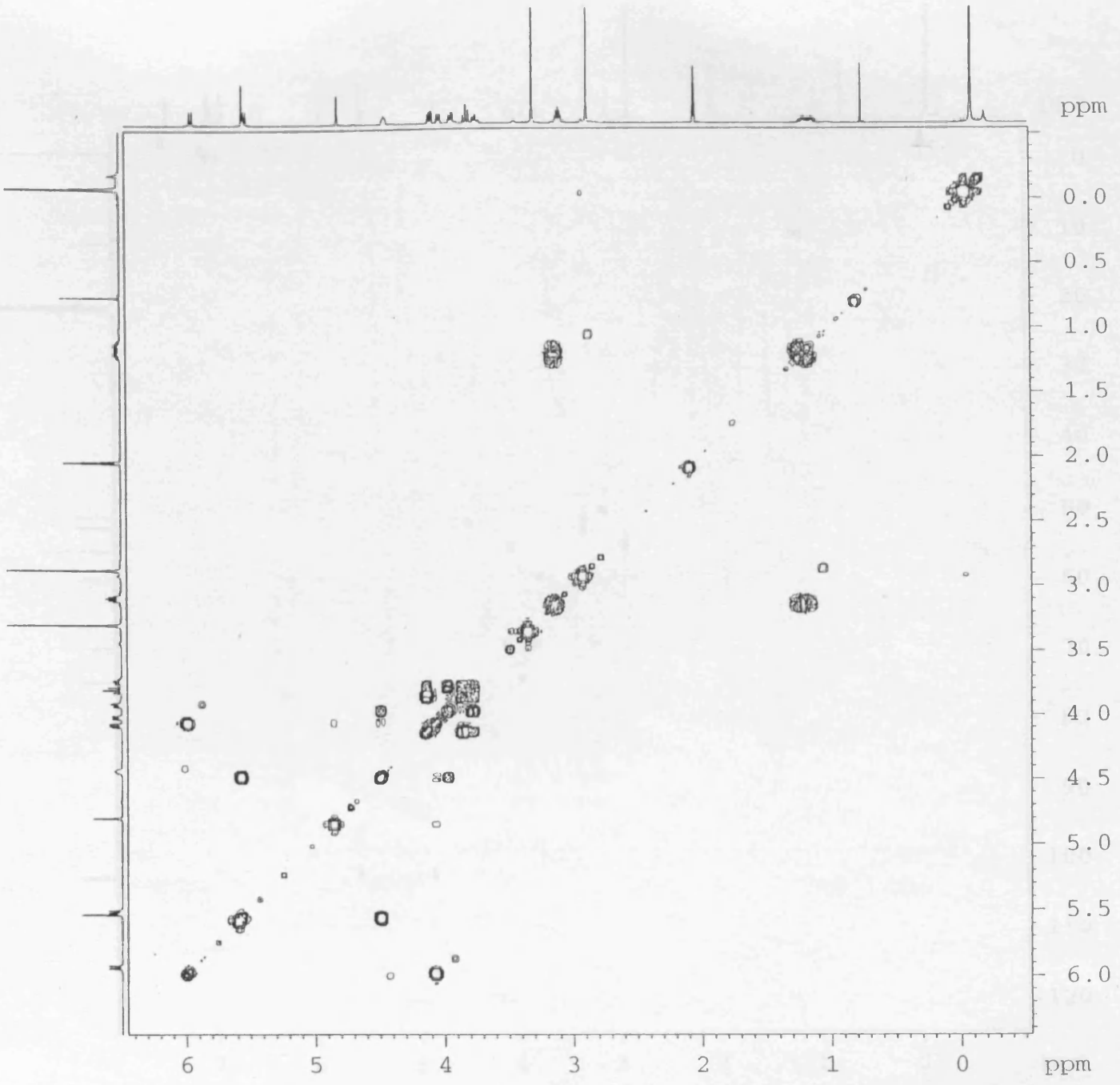
II-md-149
toluene-d8, 298 K



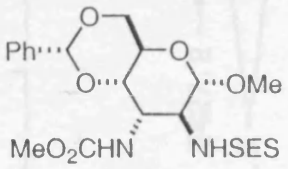
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

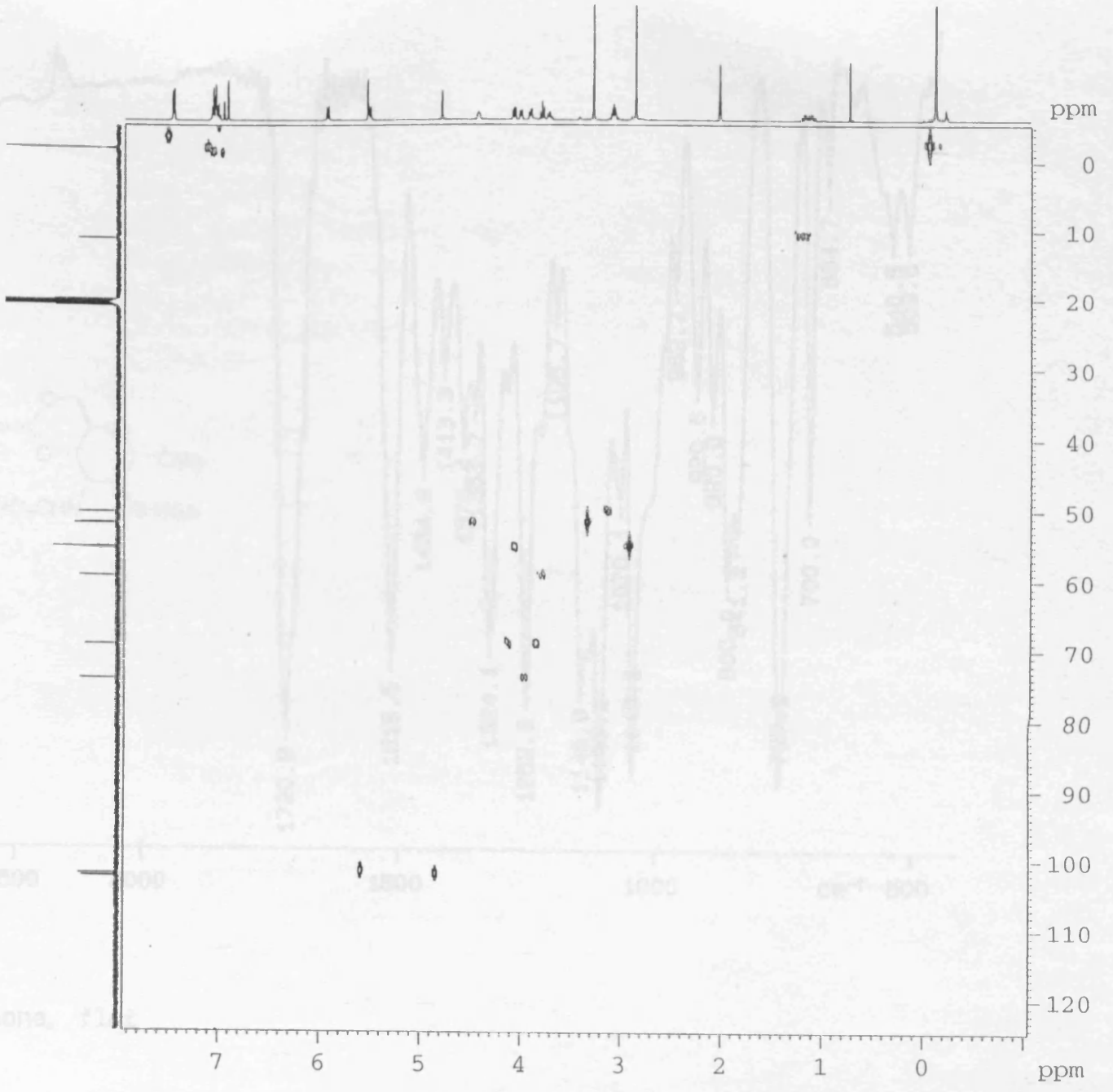
II-md-149
toluene, 298 K
COSY

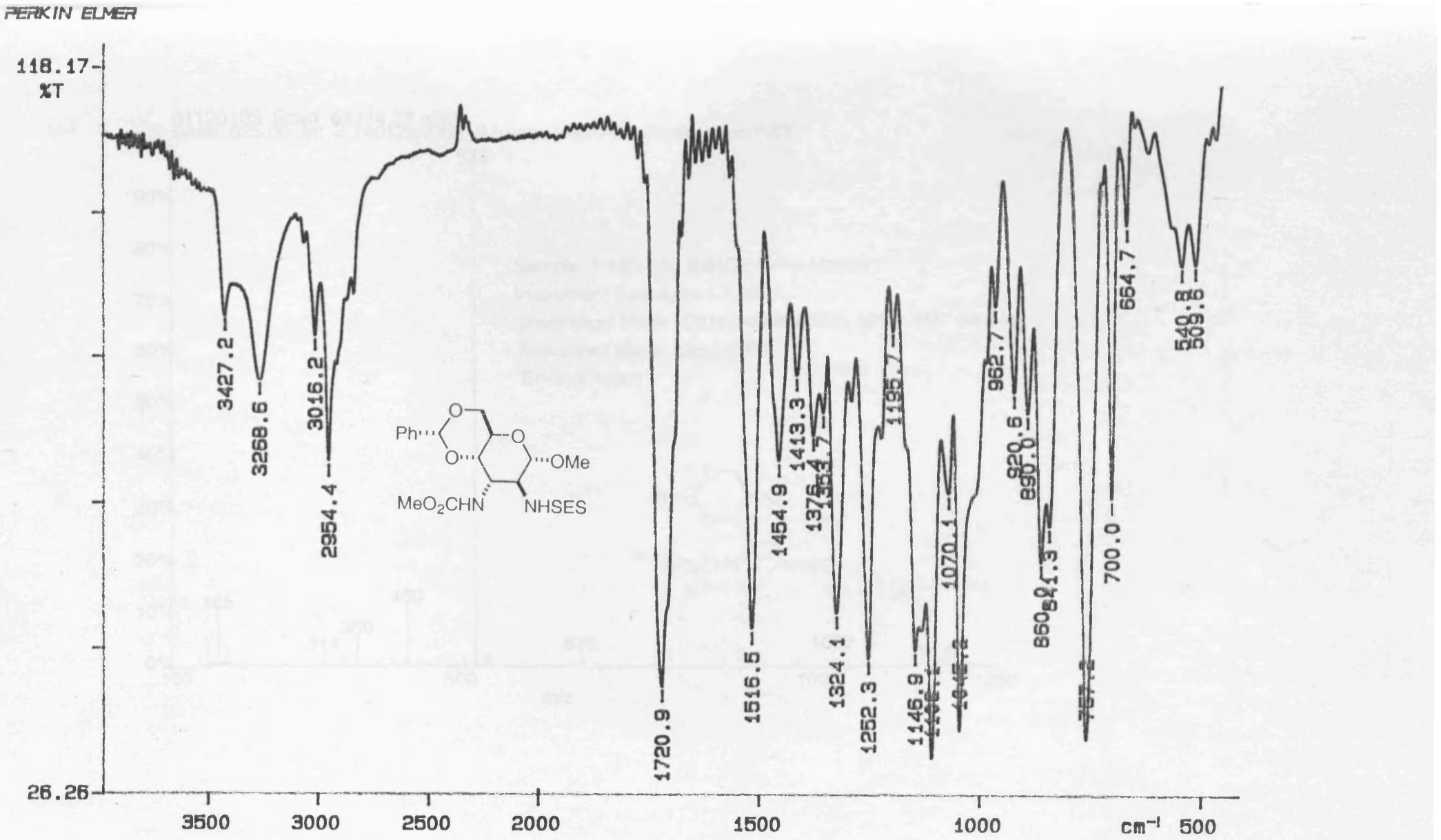




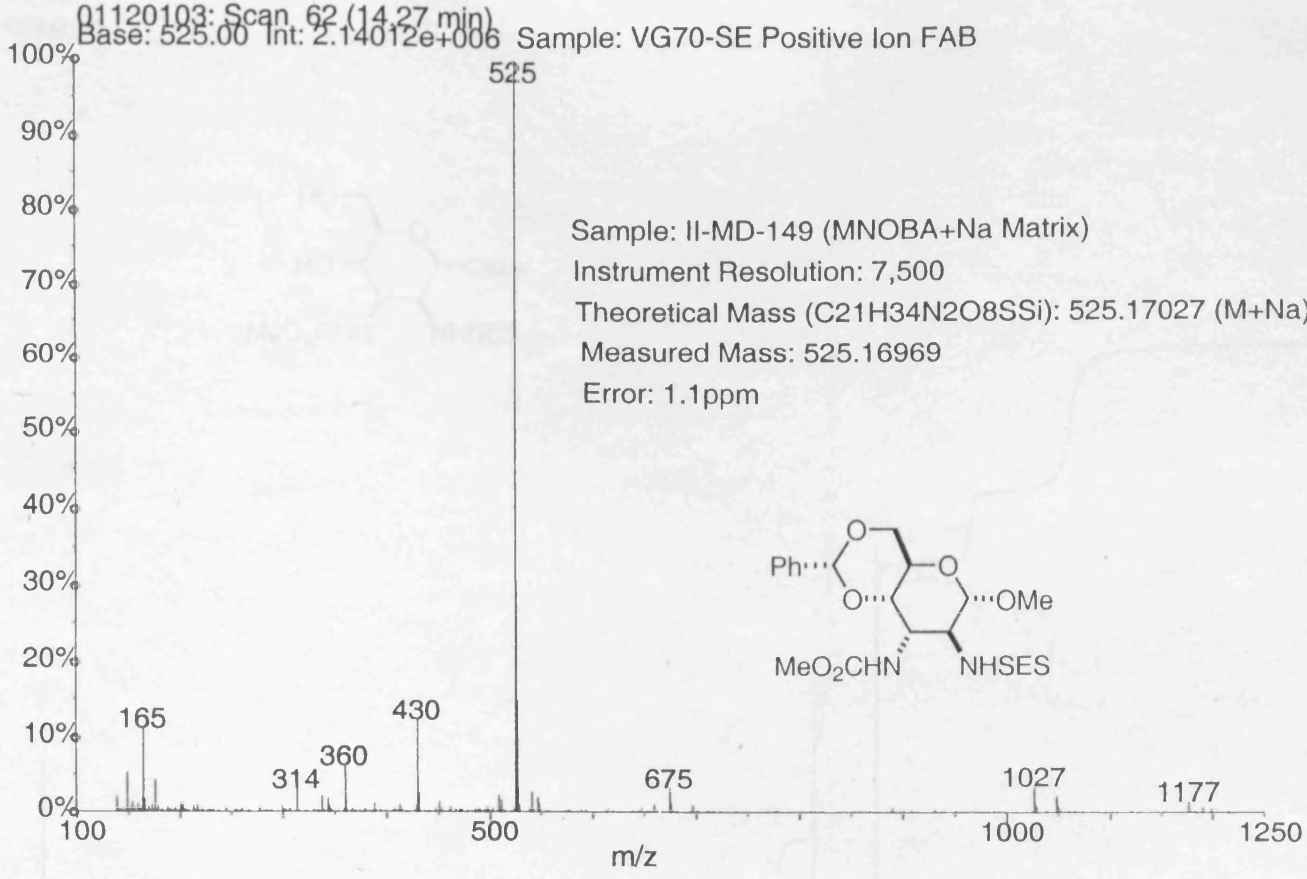
II-md-149
toluene, 298 K
HMQC



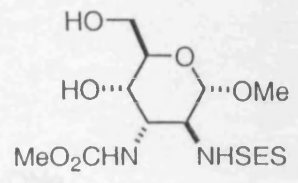




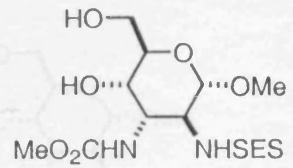
02/10/30 14:36
X: 64 scans, 16.0cm-1, apod none, flat


01120103: Scan 62 (14.27 min)
Base: 525.00 Int: 2.14012e+006
Sample: VG70-SE Positive Ion FAB
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
525
165
314
360
430
675
1027
1177
100
500
1000
1250
m/z
Sample: II-MD-149 (MNOBA+Na Matrix)
Instrument Resolution: 7,500
Theoretical Mass (C21H34N2O8SSi): 525.17027 (M+Na)
Measured Mass: 525.16969
Error: 1.1ppm
Ph
O
O
O
OMe
MeO2CHN
NHSES

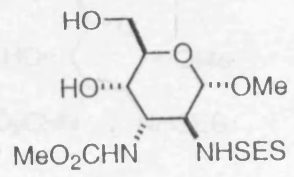
II-md-151
CDCl3, 298 K

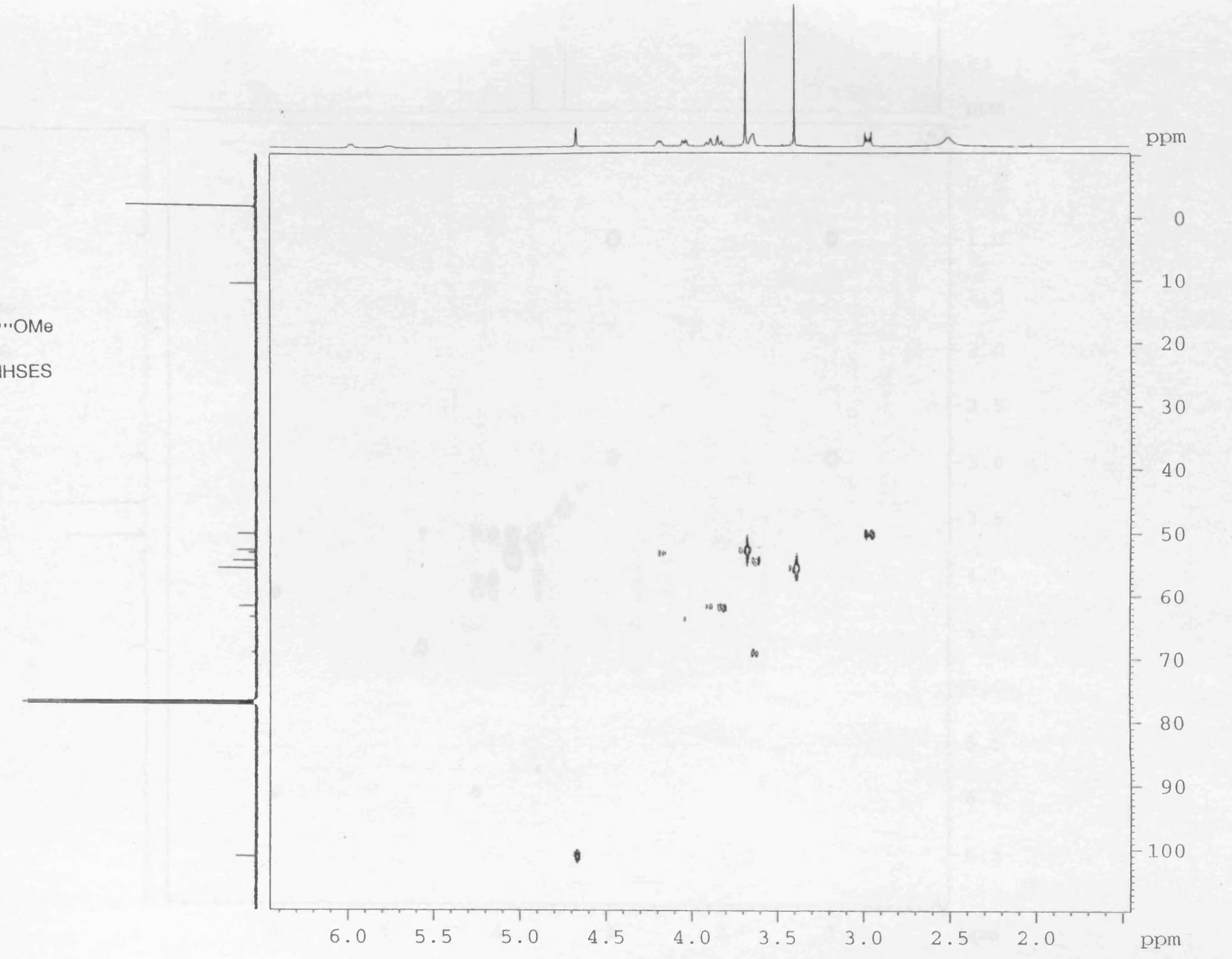


II-md-151
CDCl3, 298 K

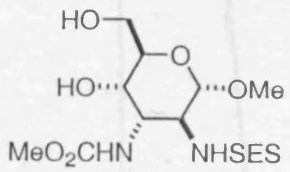


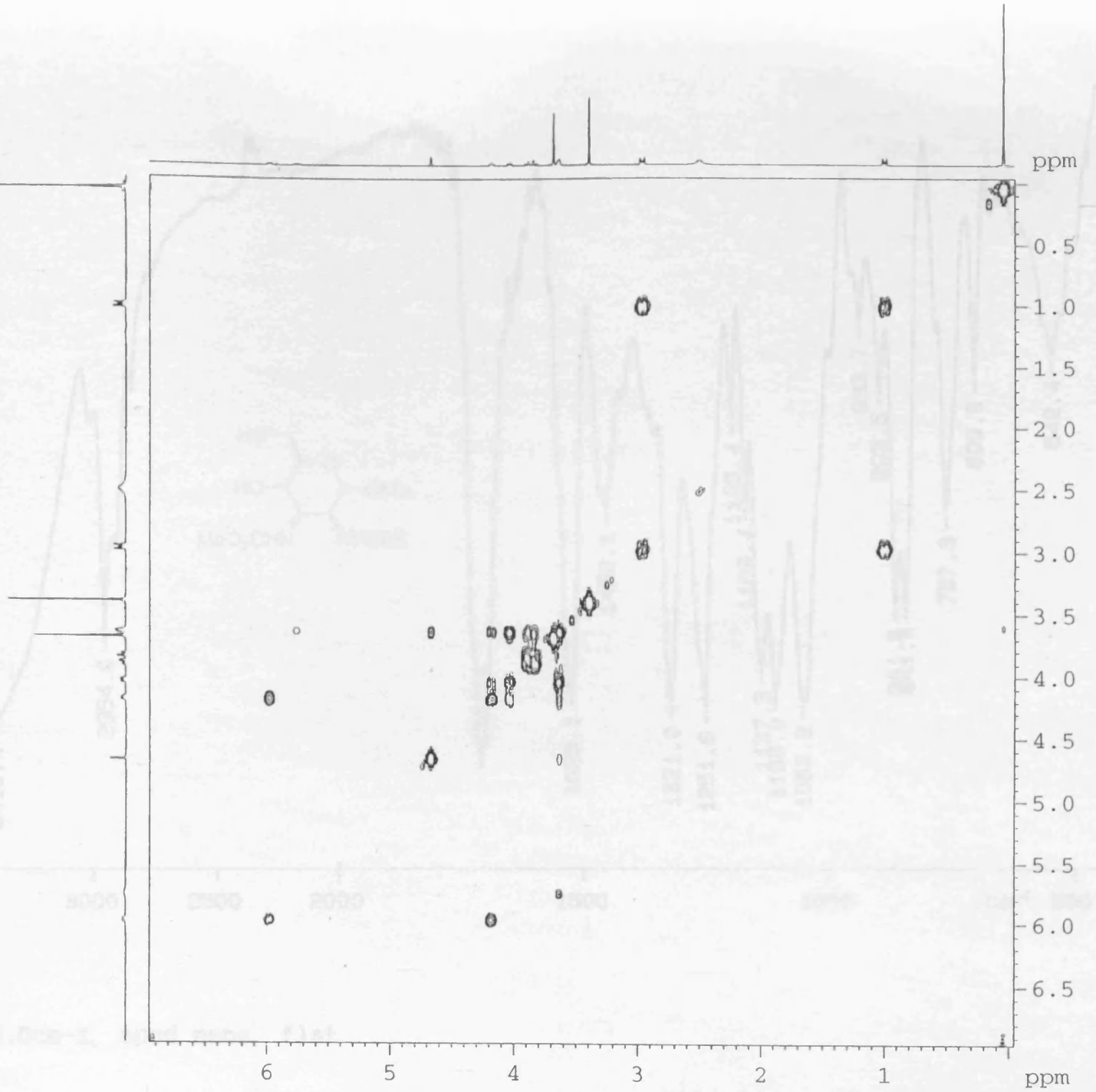
II-md-151
CDCl3, 298 K
HMQC

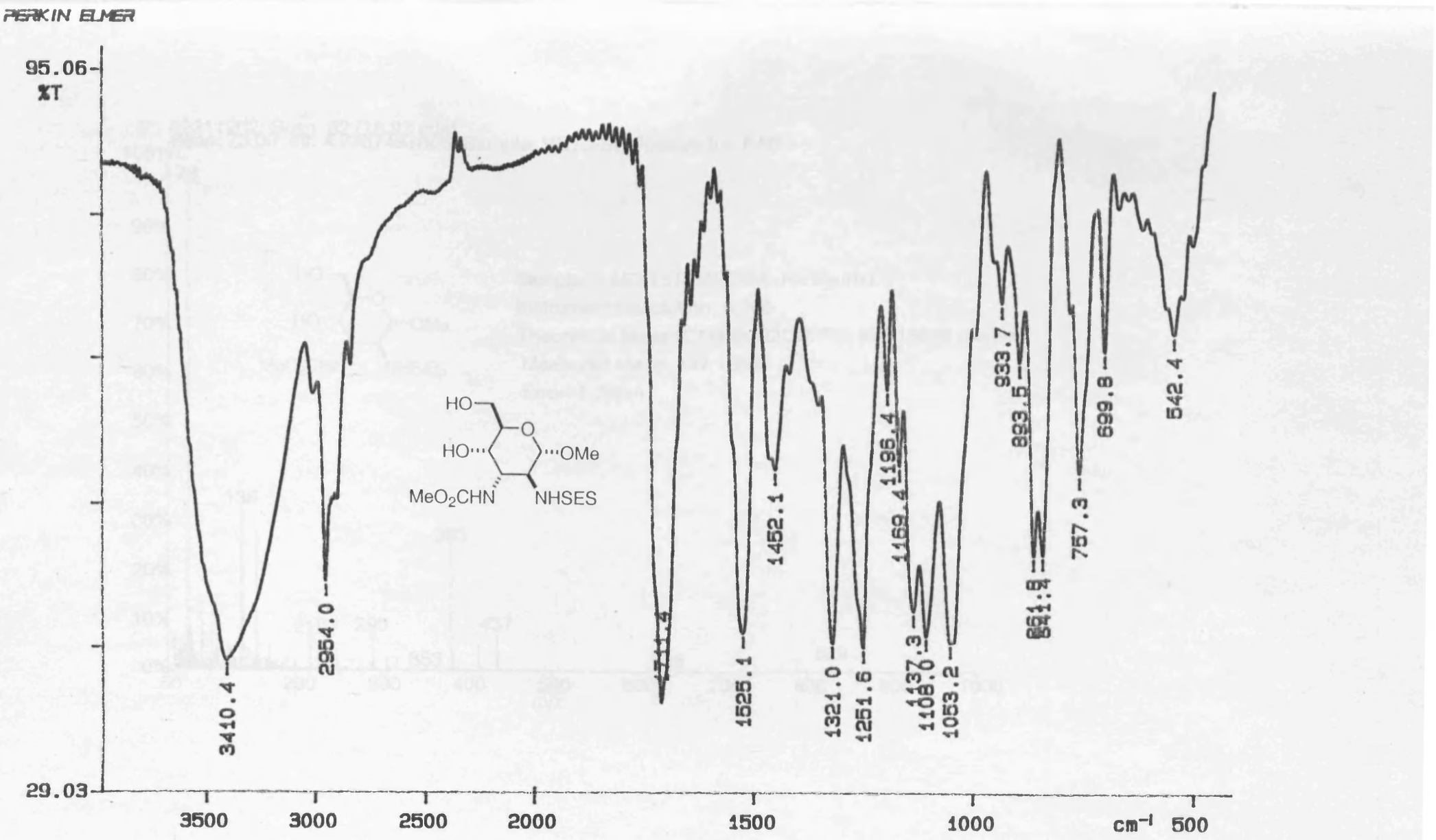




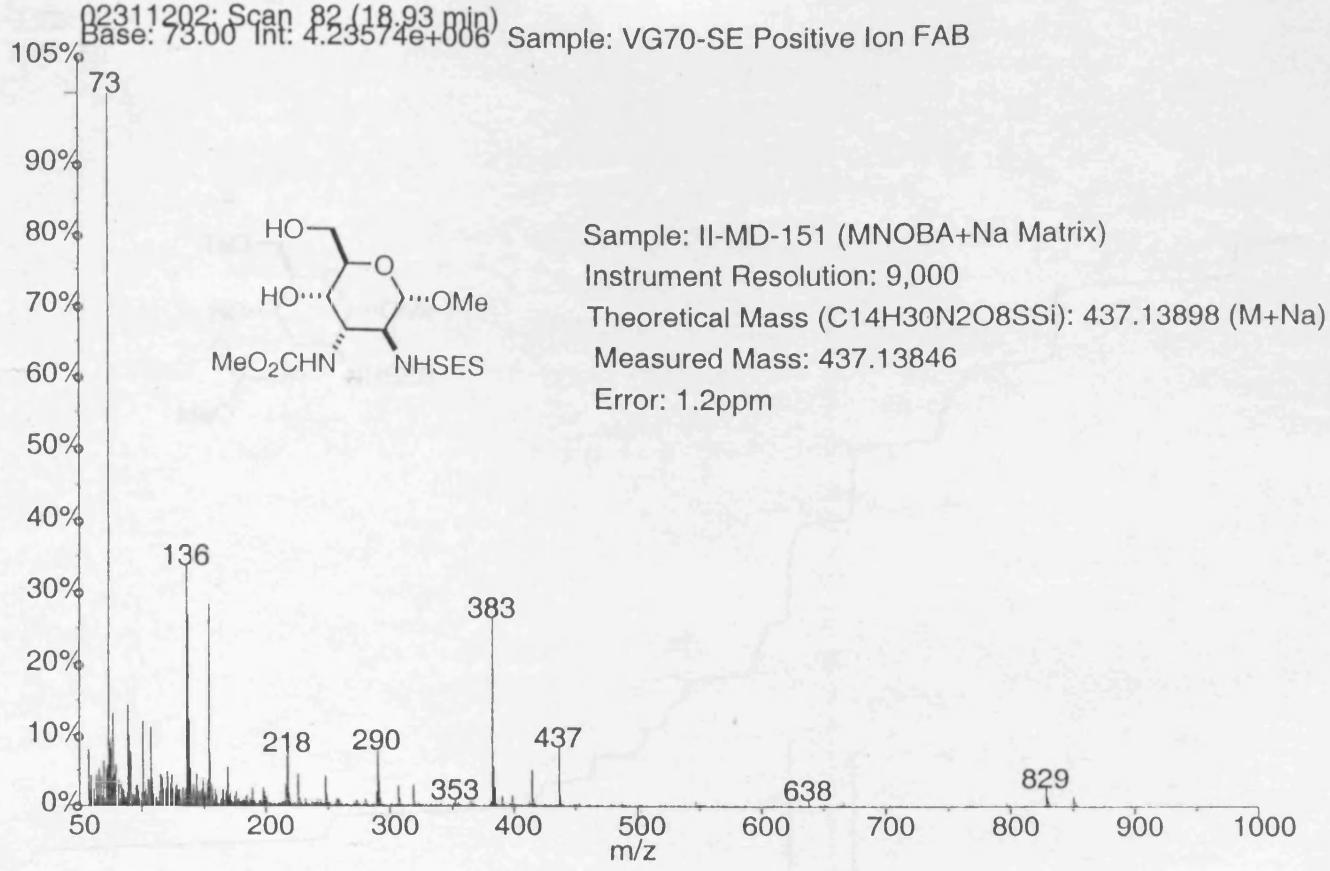
II-md-151
CDC13, 298 K
COSY



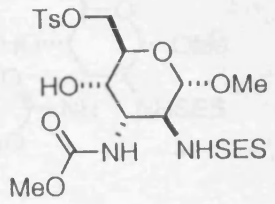




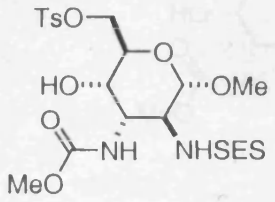
02/10/30 14:51
X: 64 scans, 16.0cm-1, apod none, flat


02311202: Scan 82 (18.93 min)
Base: 73.00 Int: 4.23574e+006
Sample: VG70-SE Positive Ion FAB
105%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
73
136
383
218
290
437
353
638
829
50
200
300
400
500
600
700
800
900
1000
m/z
HO
O
HO
OMe
MeO2CHN
NHSES
Sample: II-MD-151 (MNOBA+Na Matrix)
Instrument Resolution: 9,000
Theoretical Mass (C14H30N2O8SSi): 437.13898 (M+Na)
Measured Mass: 437.13846
Error: 1.2ppm

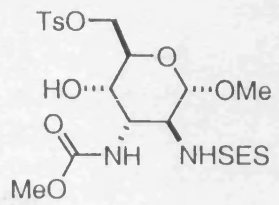
II-md-152
CDCl3, 328 K

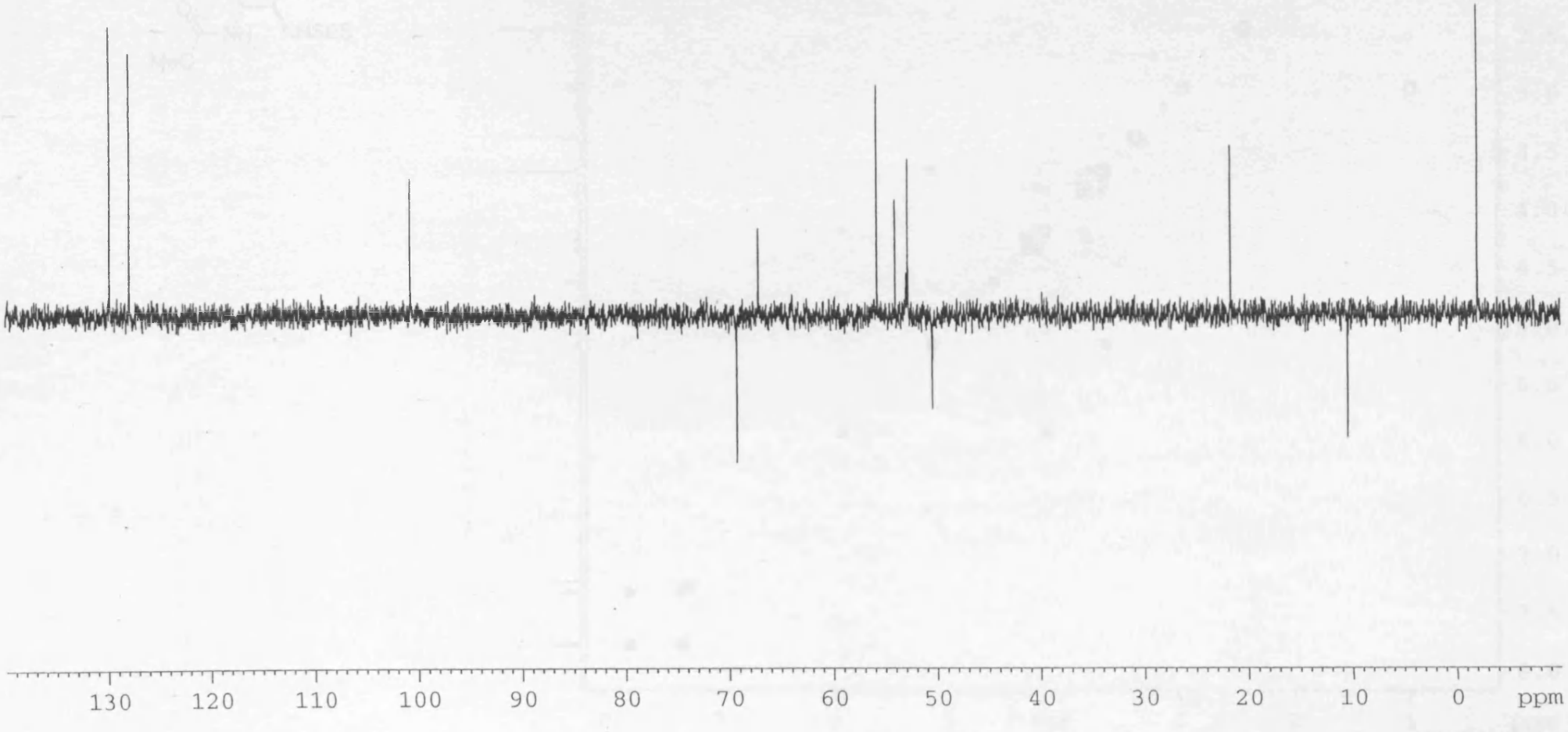


II-md-152
CDCl3, 298 K

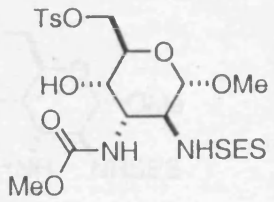


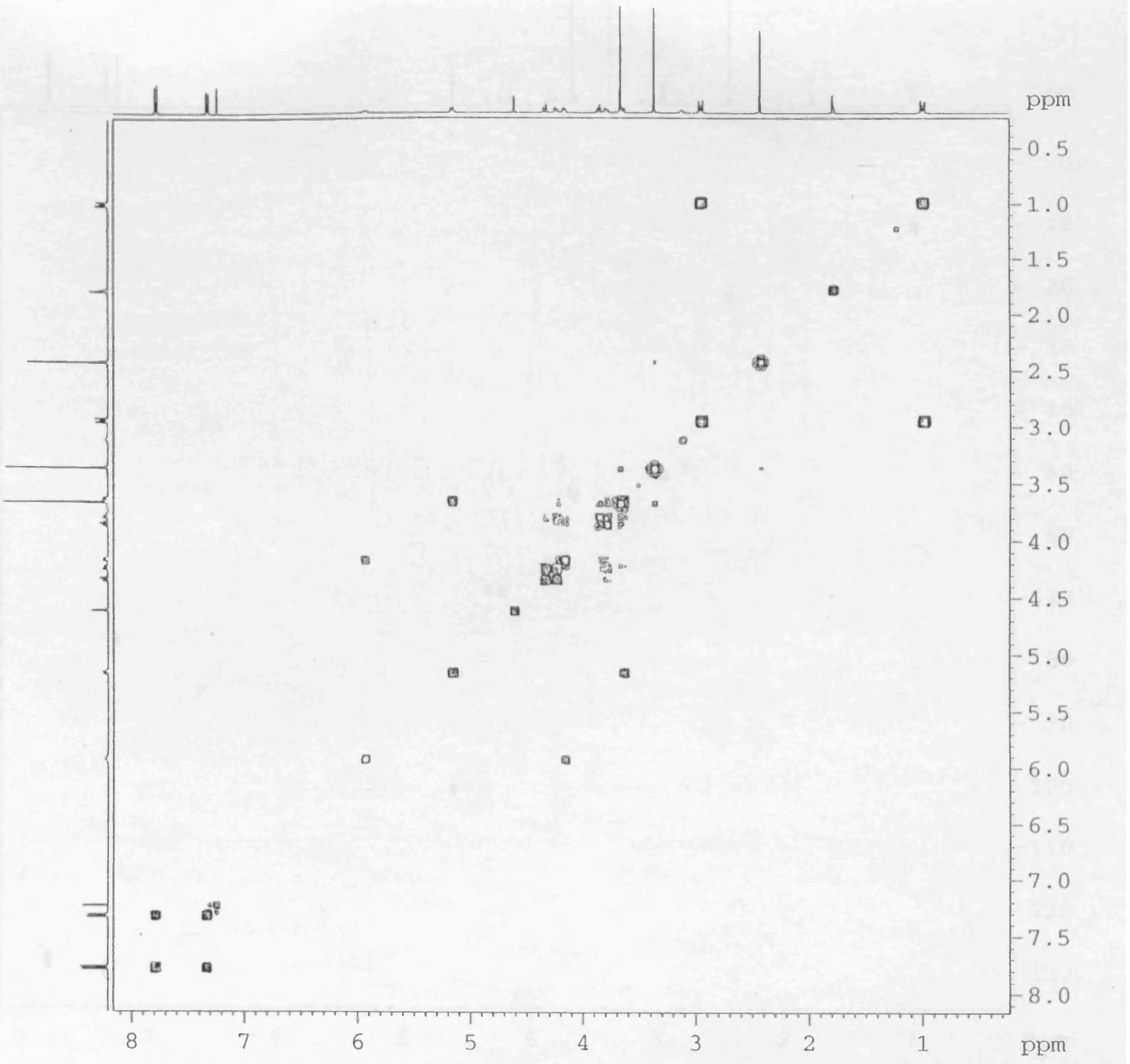
II-md-152
CDCl3, 298 K
DEPT135



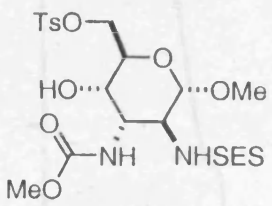


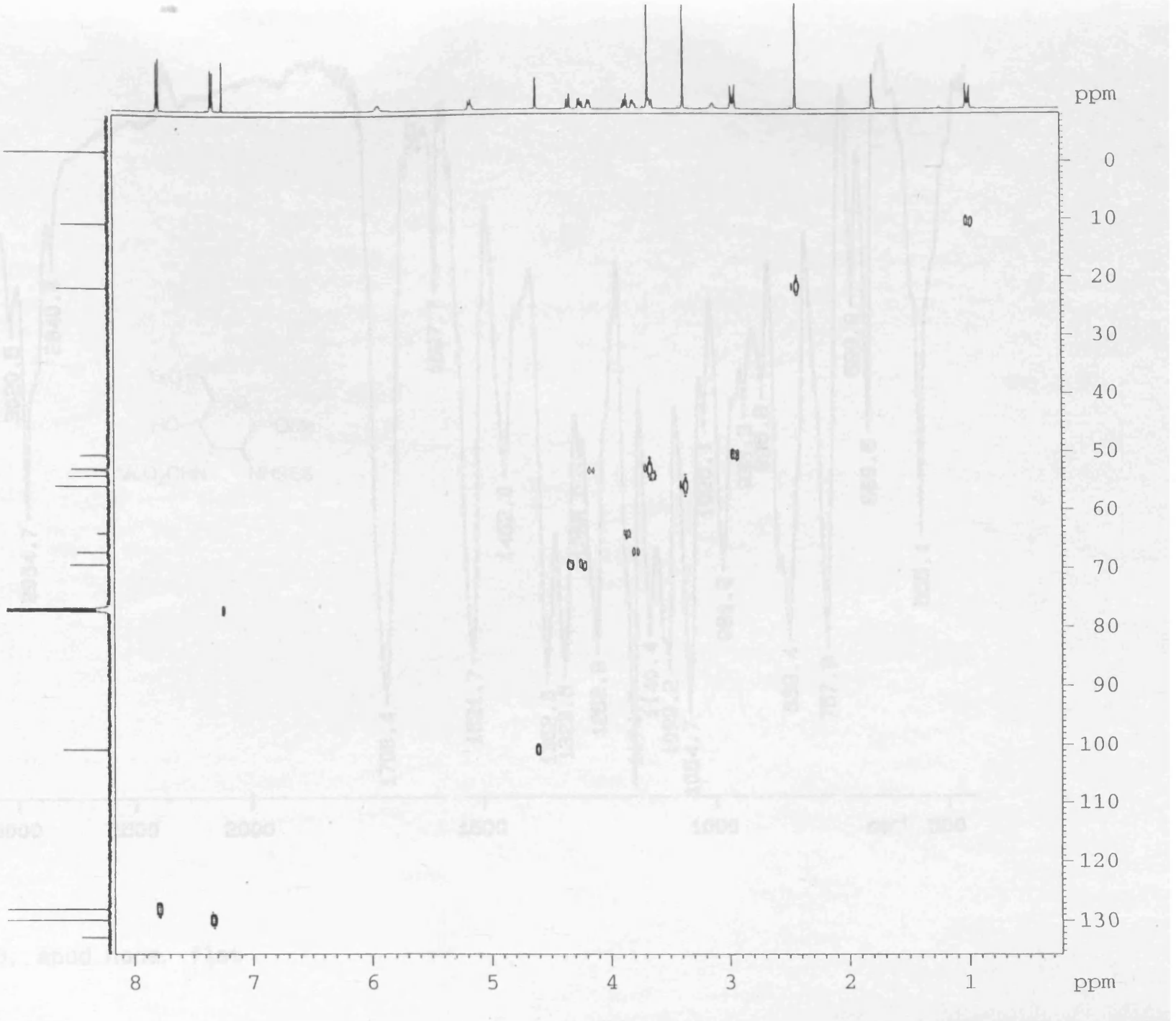
II-md-152
CDCl3, 298 K
COSY

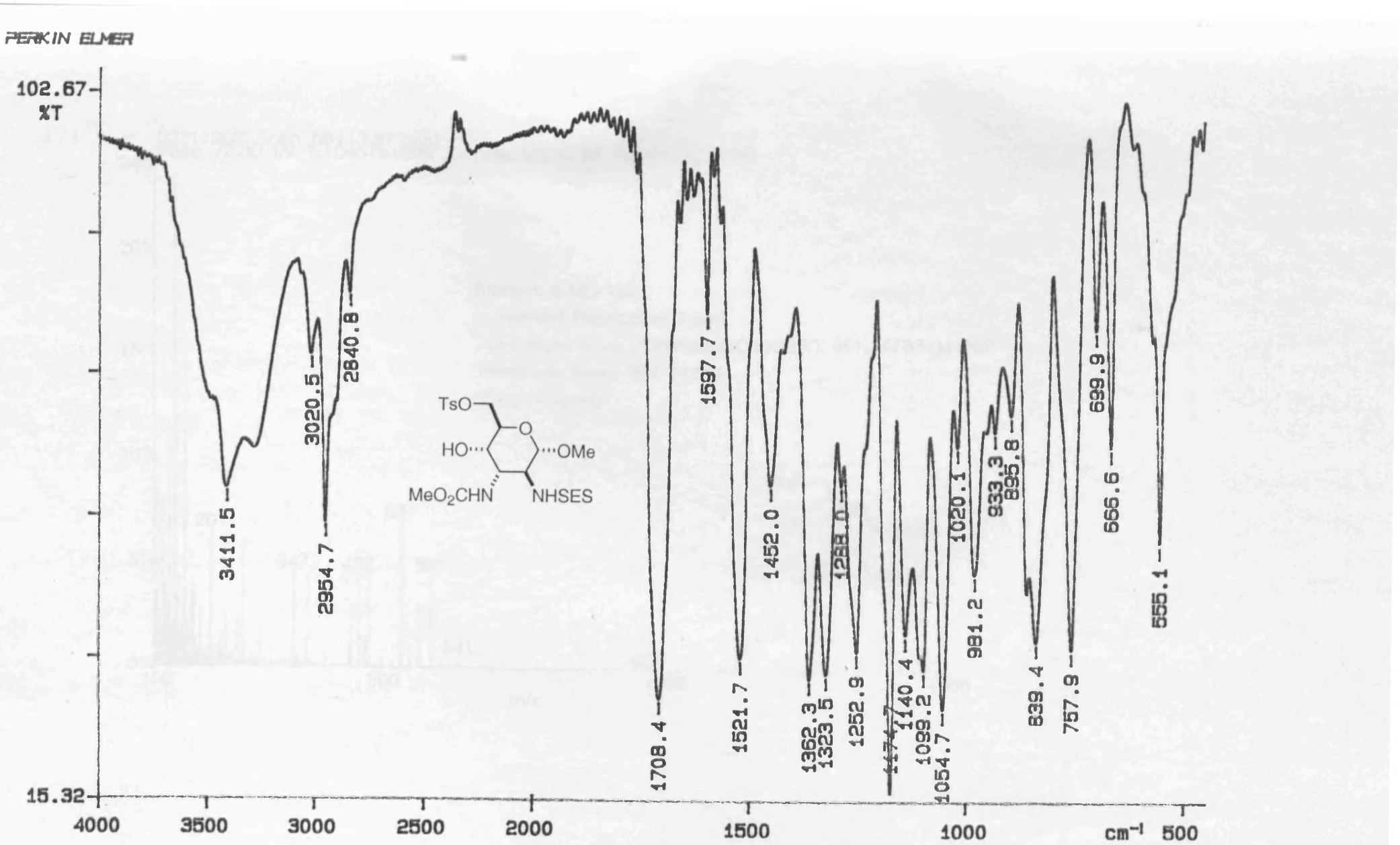




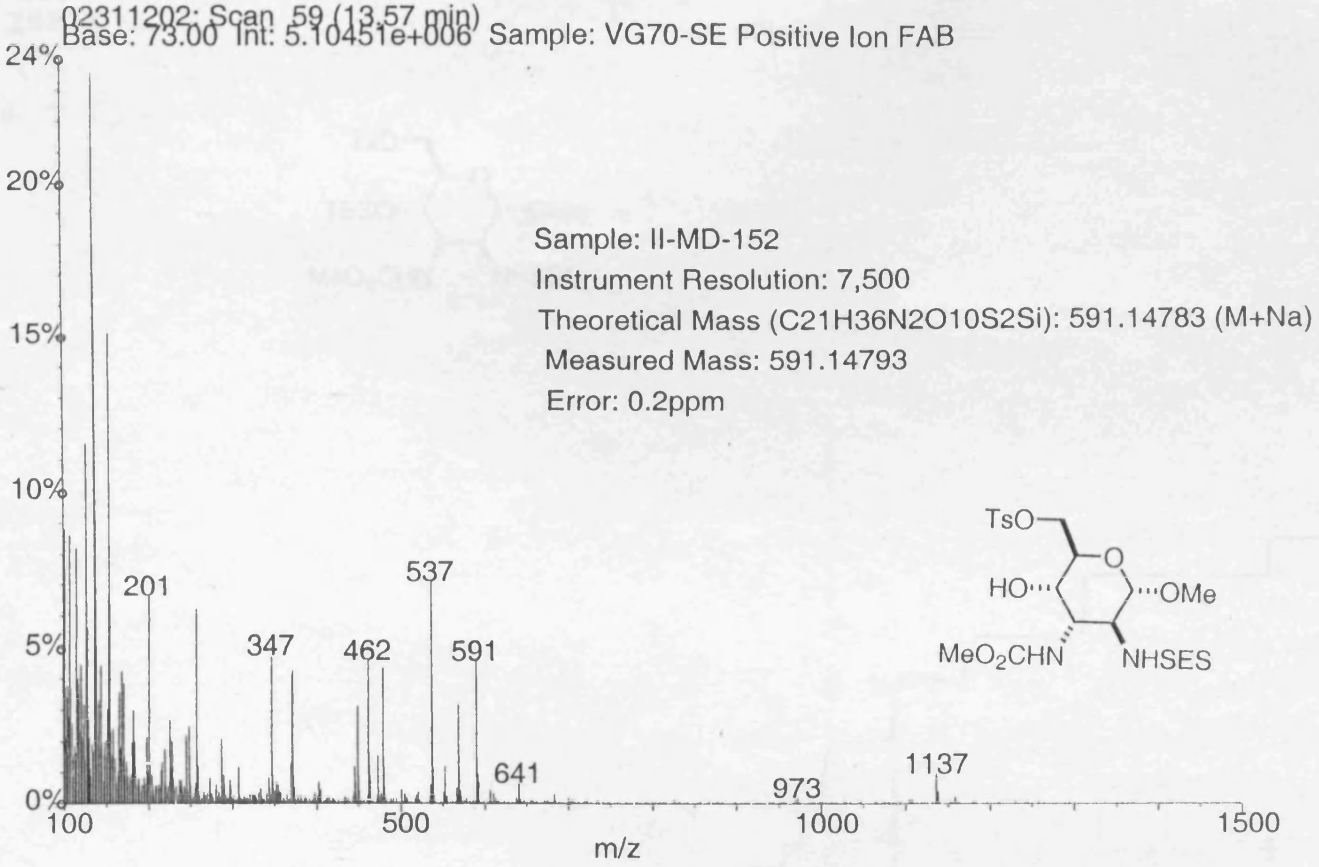
II-md-152
CDCl3, 298 K
HMQC



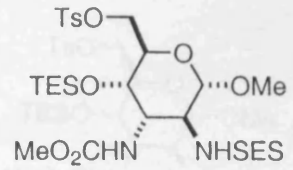




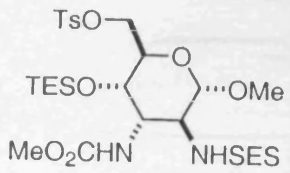
02/10/30 15: 14
X: 64 scans, 16.0cm-1, apod none, flat


02311202: Scan 59 (13.57 min)
Base: 73.00 Int: 5.10451e+006 Sample: VG70-SE Positive Ion FAB
24%
20%
15%
10%
5%
0%
201
347
462
537
591
641
973
1137
100
500
1000
1500
m/z
Sample: II-MD-152
Instrument Resolution: 7,500
Theoretical Mass (C21H36N2O10S2Si): 591.14783 (M+Na)
Measured Mass: 591.14793
Error: 0.2ppm
TsO
O
HO
OMe
MeO2CHN
NHSES

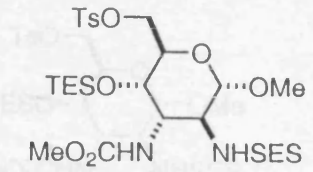
II-md-155
CDCl3, 298 K

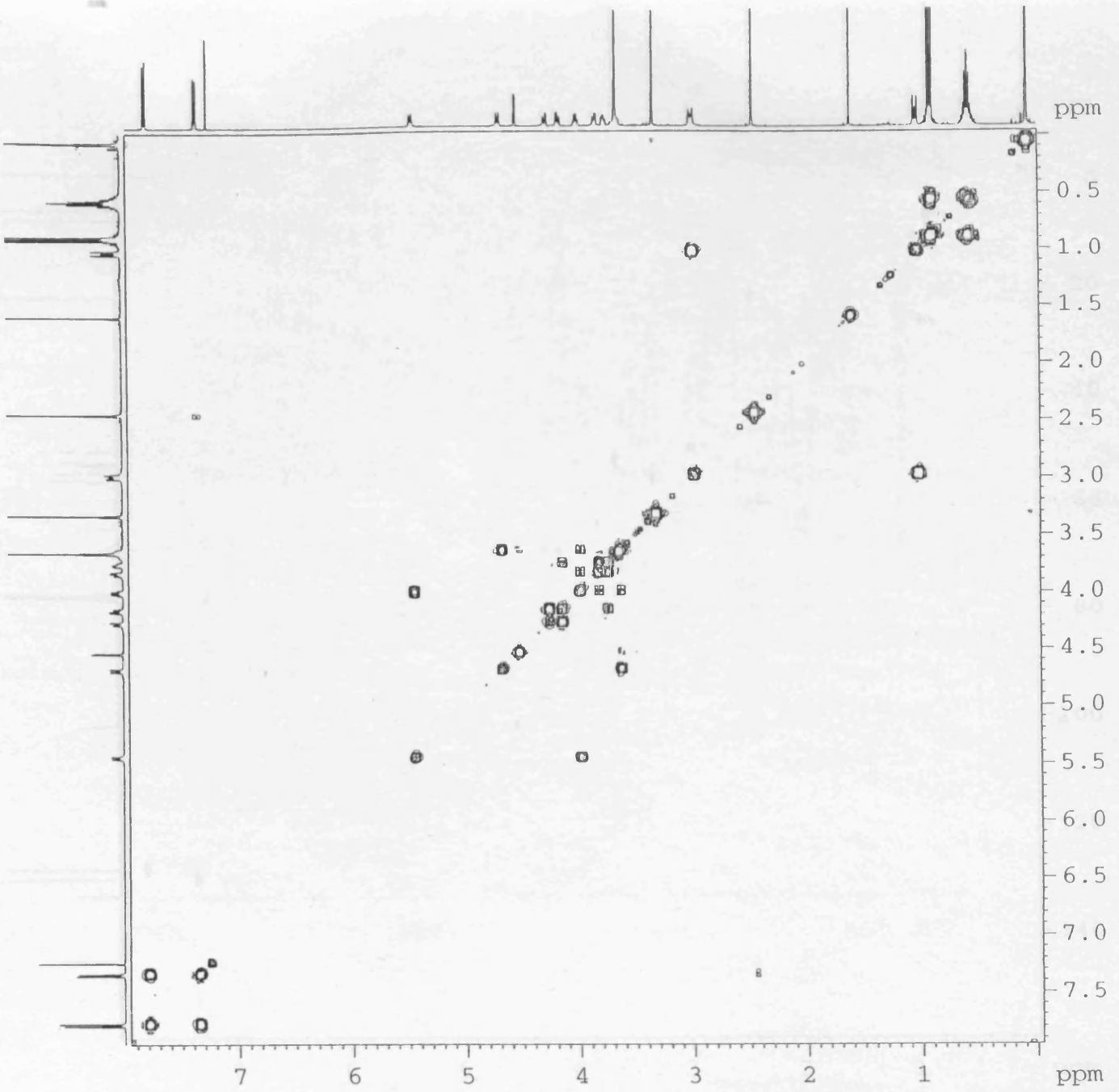


II-md-155
CDCl3, 298 K

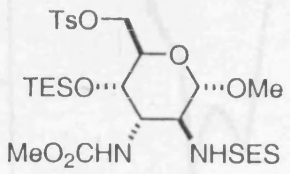


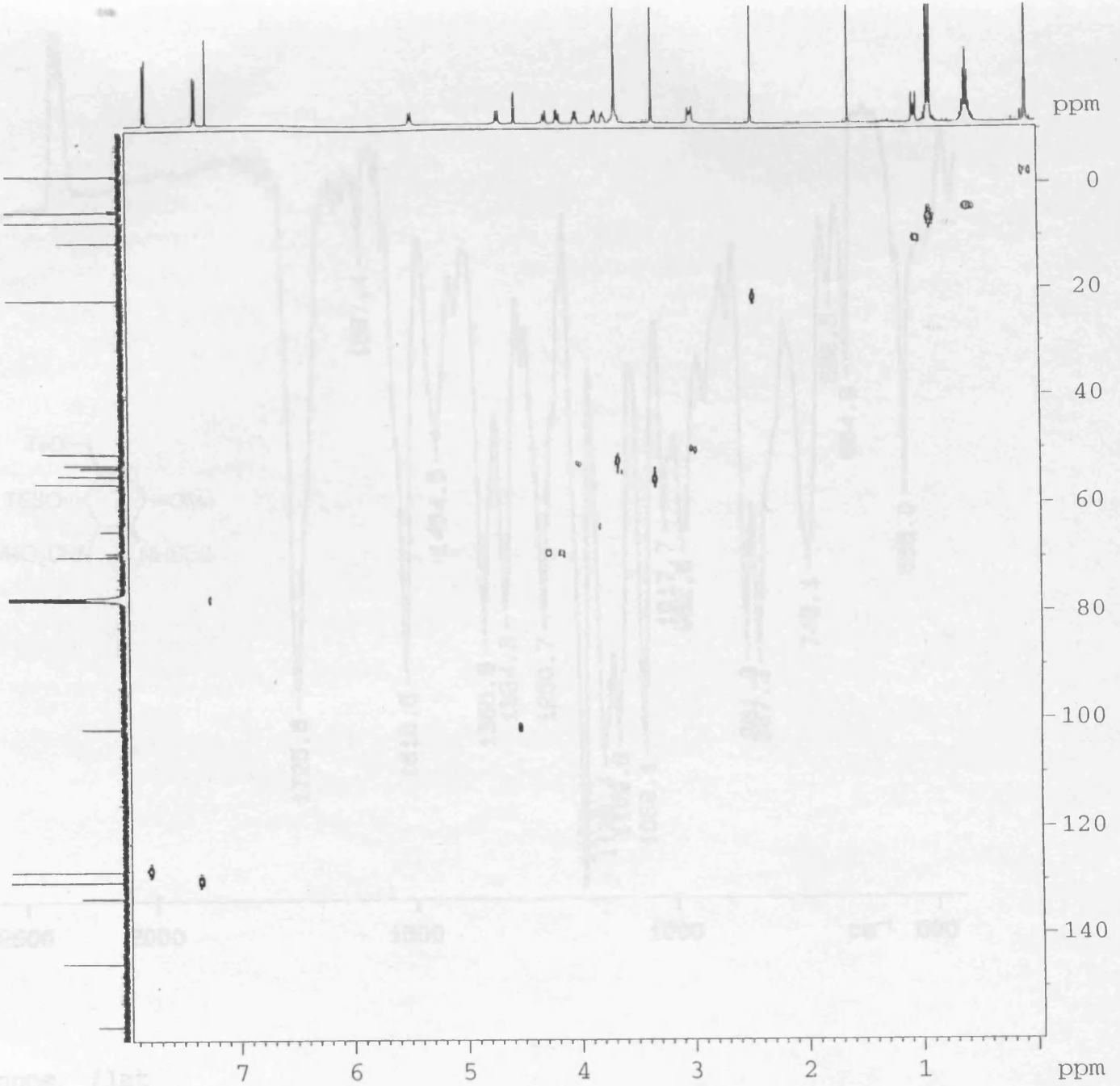
II-md-155
CDCl3, 298 K
COSY

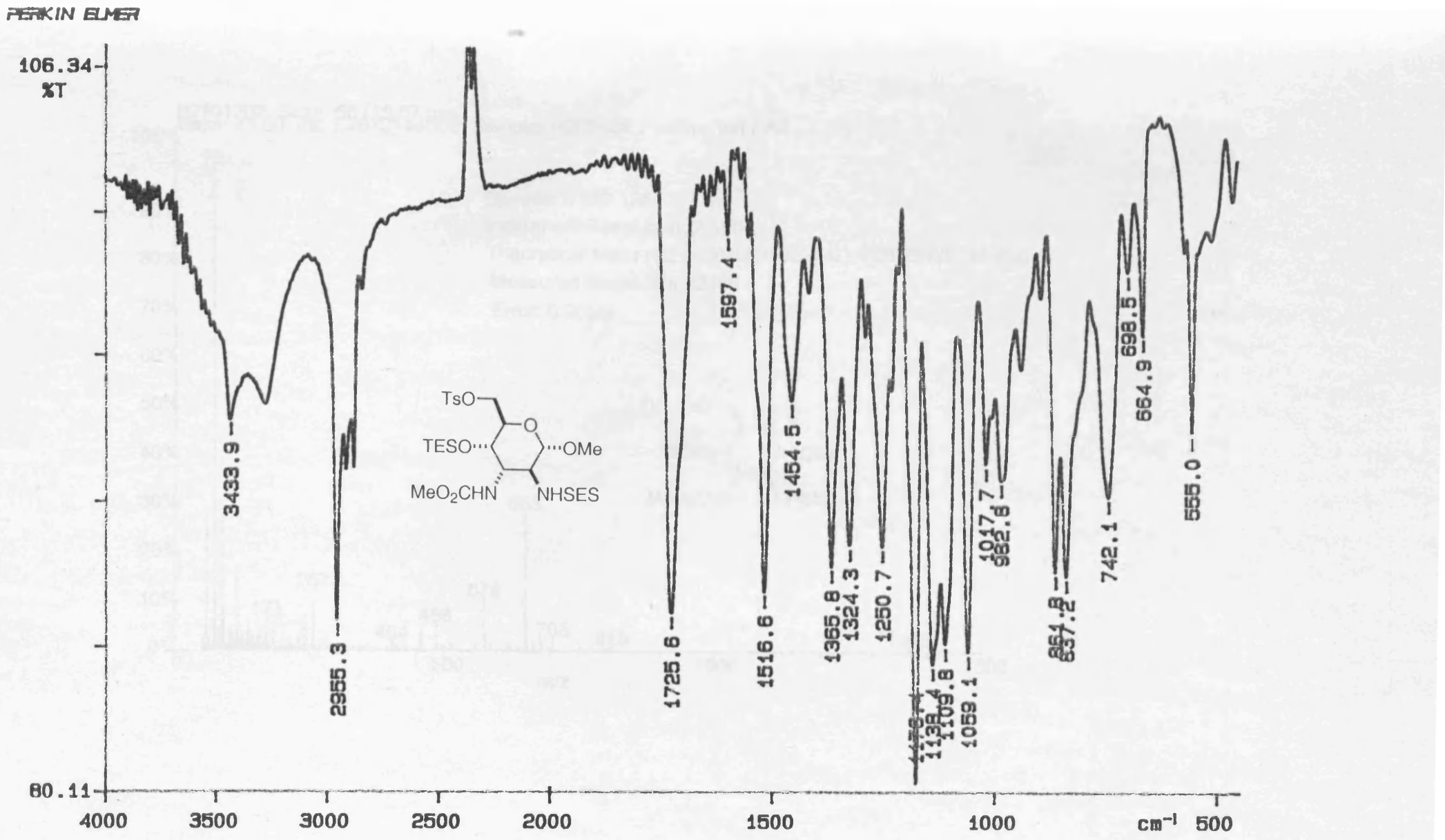




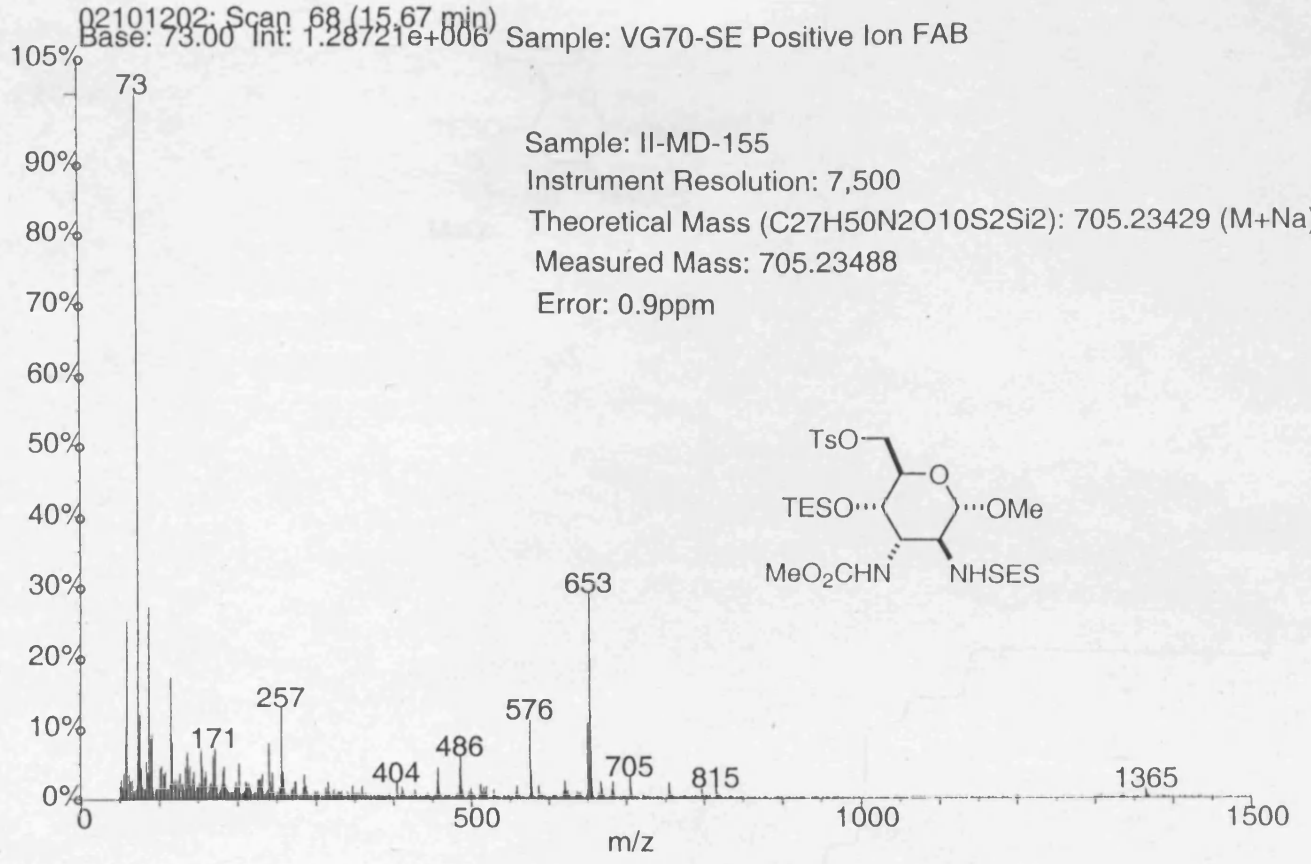
II-md-155
CDC13, 298 K



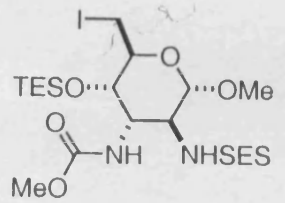




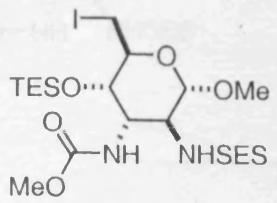
02/10/30 16:36
X: 64 scans, 16.0cm-1, apod none, flat


02101202: Scan 68 (15.67 min)
Base: 73.00 Int: 1.28721e+006
Sample: VG70-SE Positive Ion FAB
105%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
73
653
257
576
171
486
404
705
815
1365
0
500
1000
1500
m/z
Sample: II-MD-155
Instrument Resolution: 7,500
Theoretical Mass (C27H50N2O10S2Si2): 705.23429 (M+Na)
Measured Mass: 705.23488
Error: 0.9ppm
TsO
O
TESO
OMe
MeO2CHN
NHSES

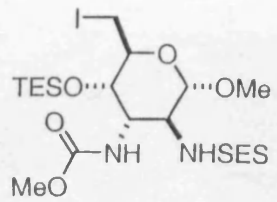
II-md-157
CDCl3, 298 K

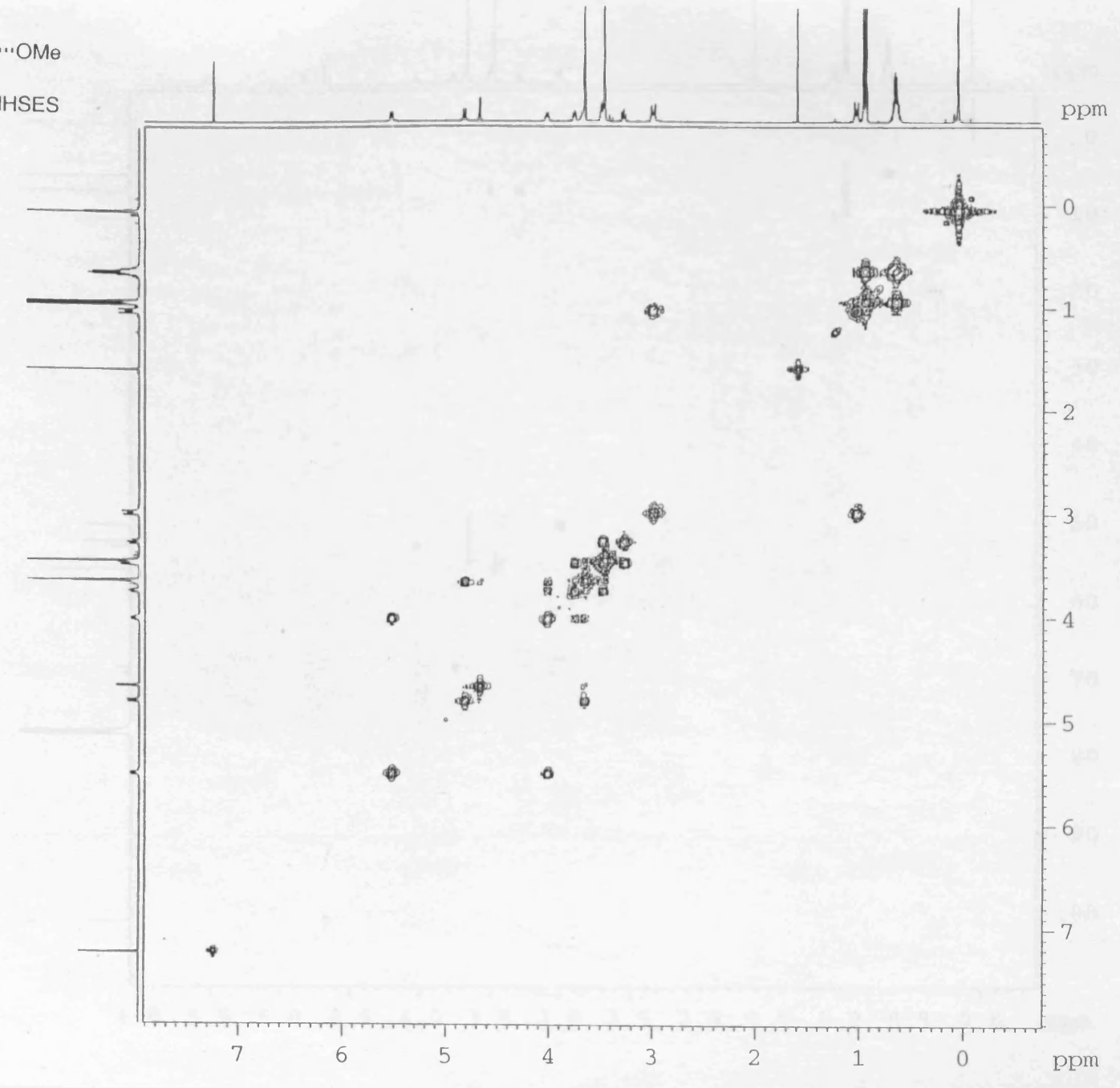


II-md-157
CDCl3, 298 K

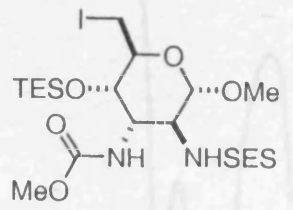


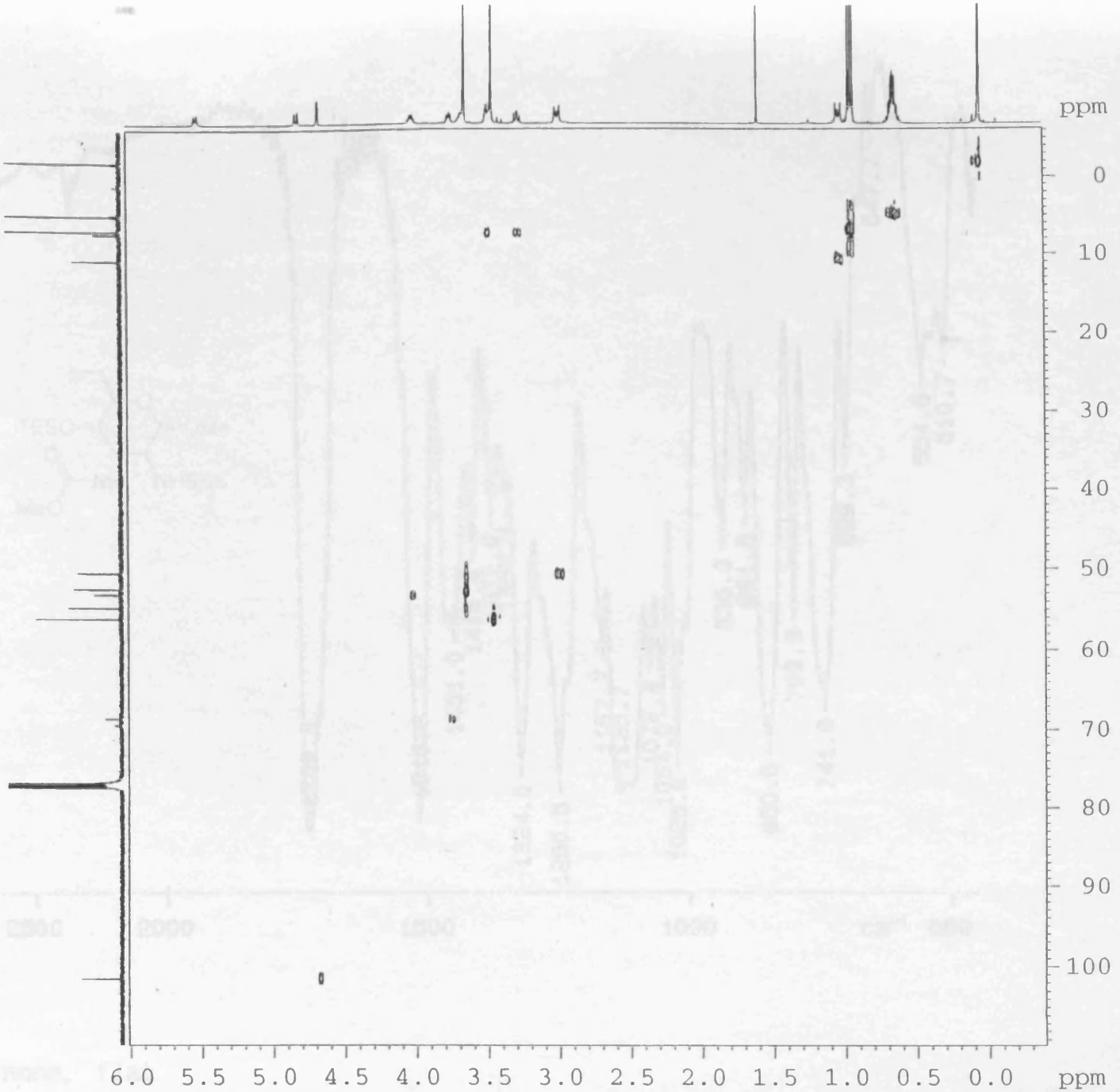
II-md-157
CDCl3, 298 K
COSY



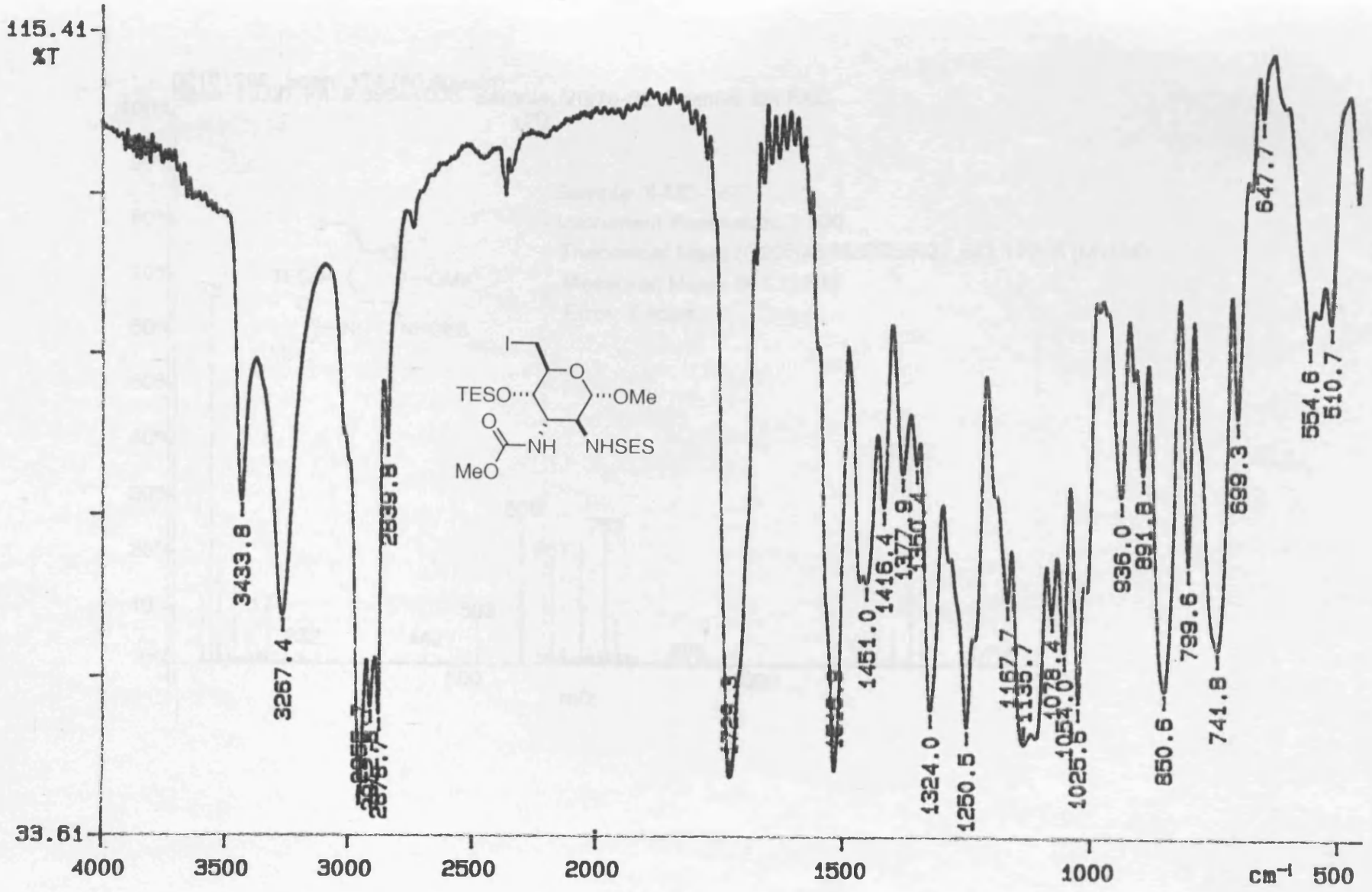


II-md-157
CDCl3, 298 K
HMQC

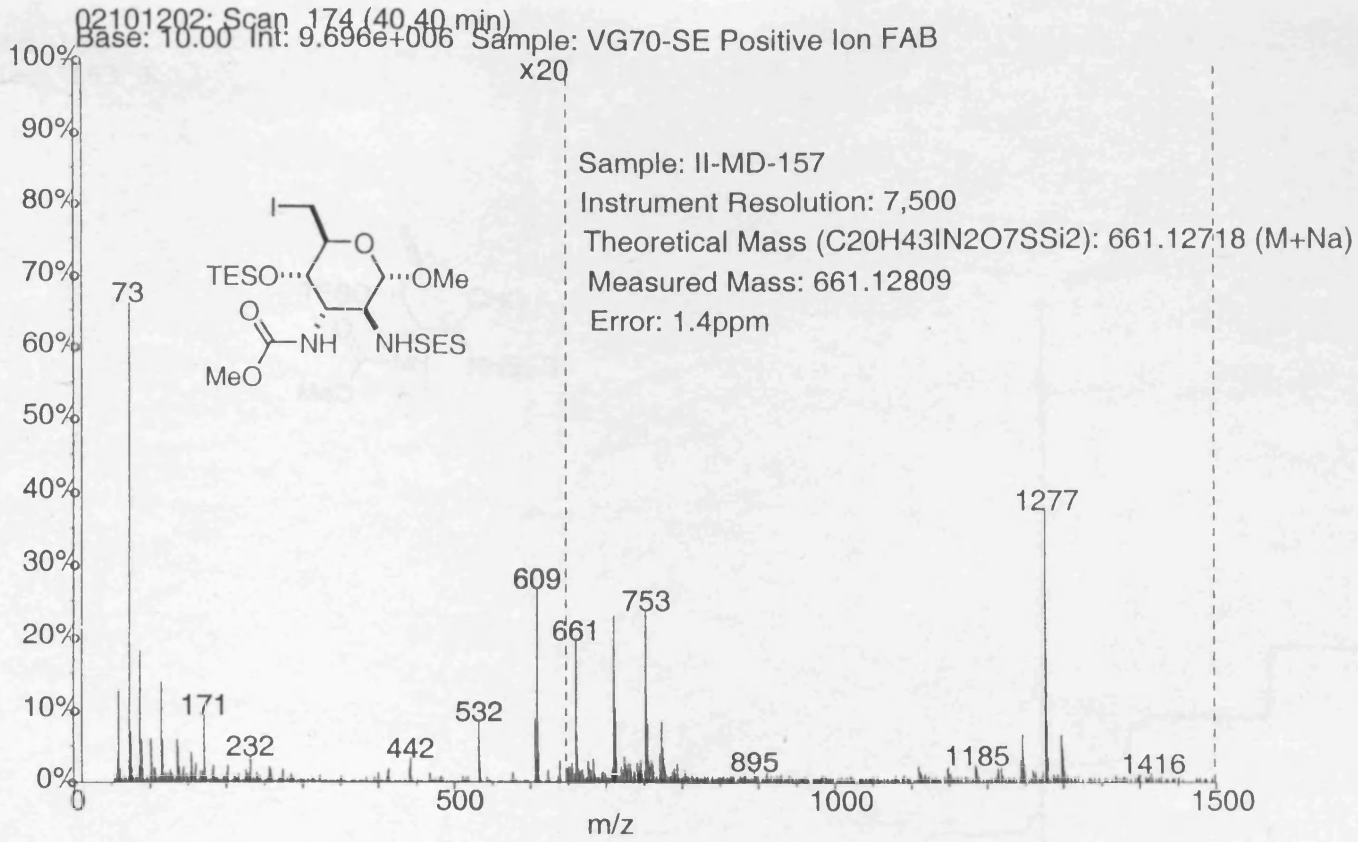




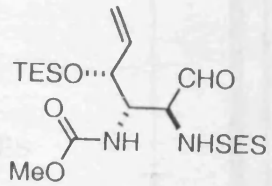
PERKIN ELMER



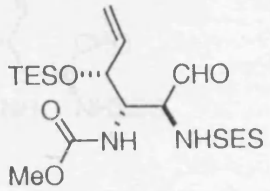
02/10/30 16: 47
X: 64 scans, 16.0cm-1, apod none, flat


02101202: Scan 174 (40.40 min)
Base: 10.00 Int: 9.696e+006 Sample: VG70-SE Positive Ion FAB
x20
Sample: II-MD-157
Instrument Resolution: 7,500
Theoretical Mass (C20H43IN2O7SSi2): 661.12718 (M+Na)
Measured Mass: 661.12809
Error: 1.4ppm
TESO
OMe
NH
NHSES
MeO
I
O
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
73
171
232
442
532
609
661
753
895
1185
1277
1416
0
500
1000
1500
m/z

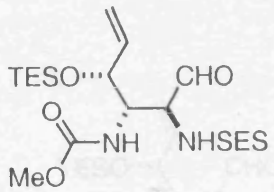
II-md-158
toluene, 363 K

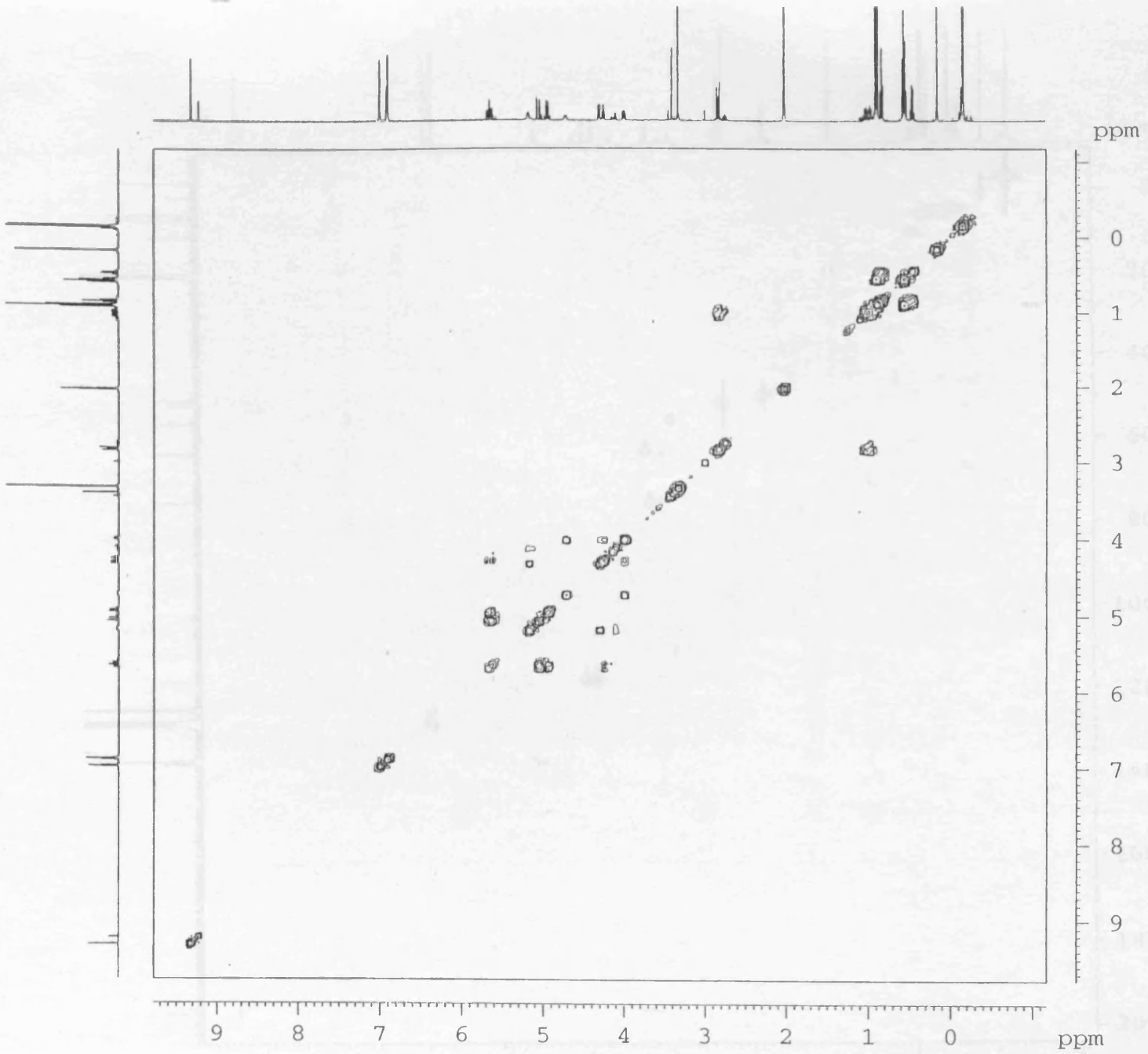


II-md-158
toluene, 363 K

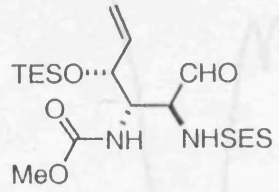


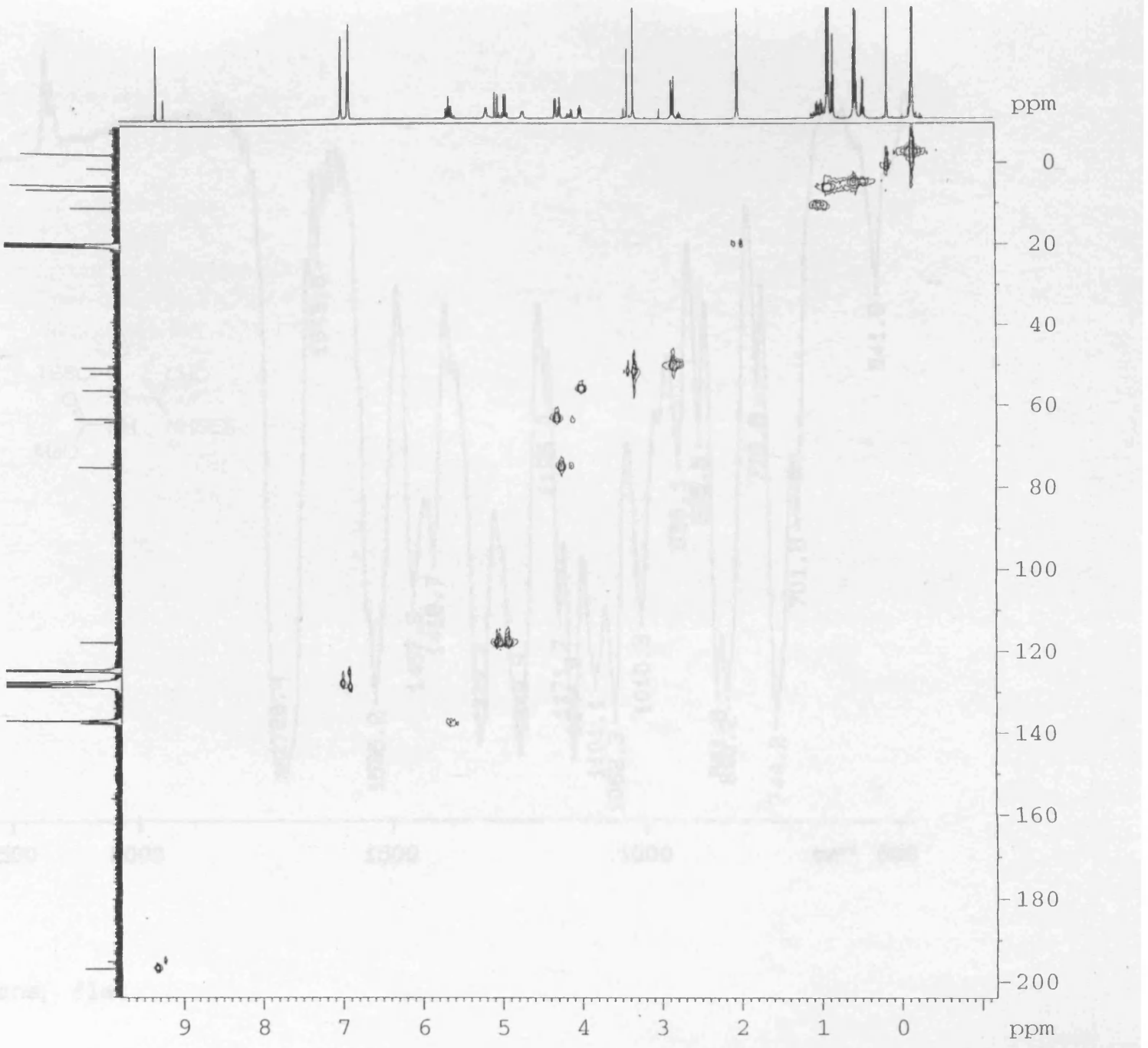
II-md-158
toluene, 363 K



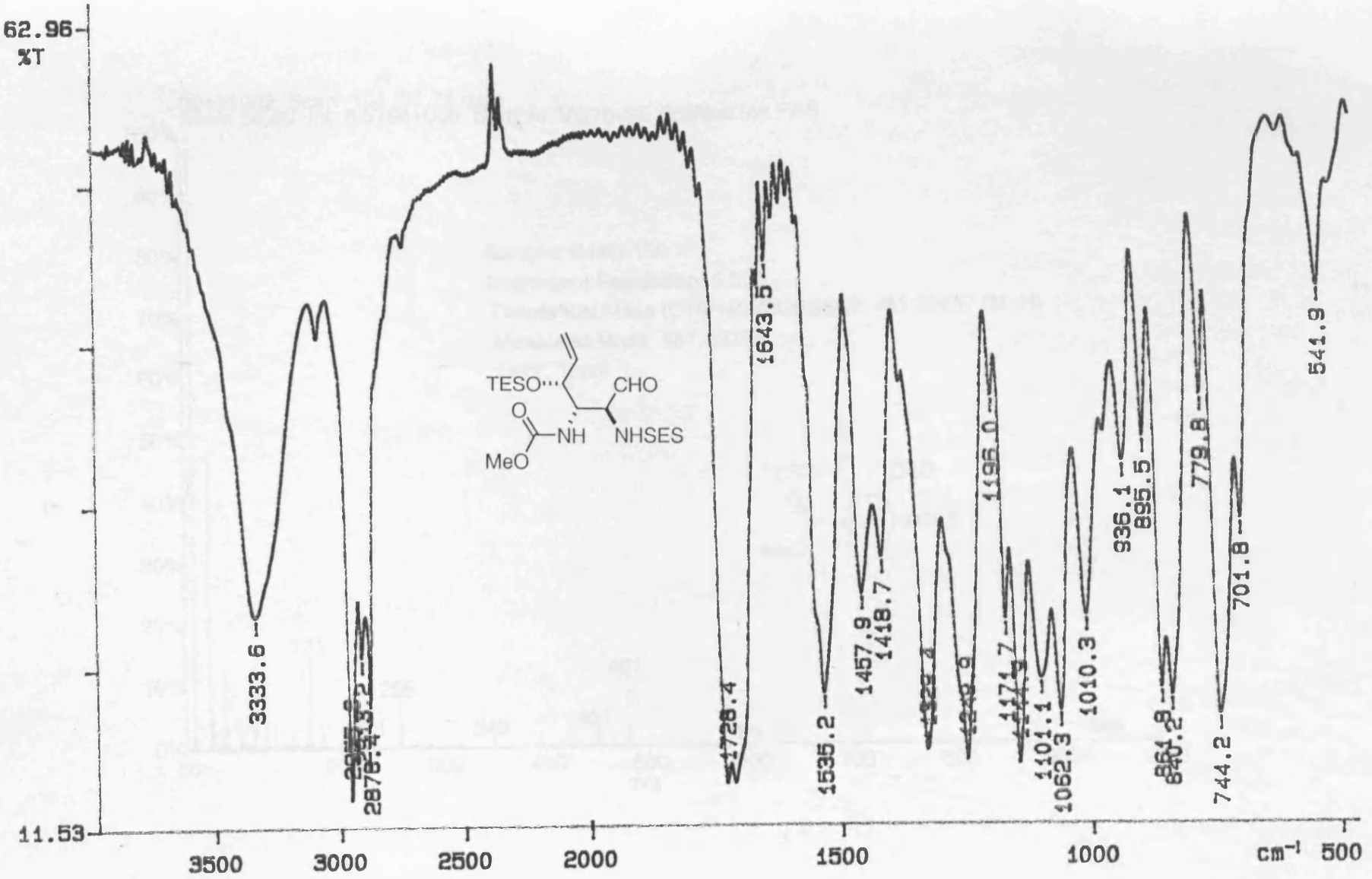


II-md-158
toluene, 363 K
HMQC

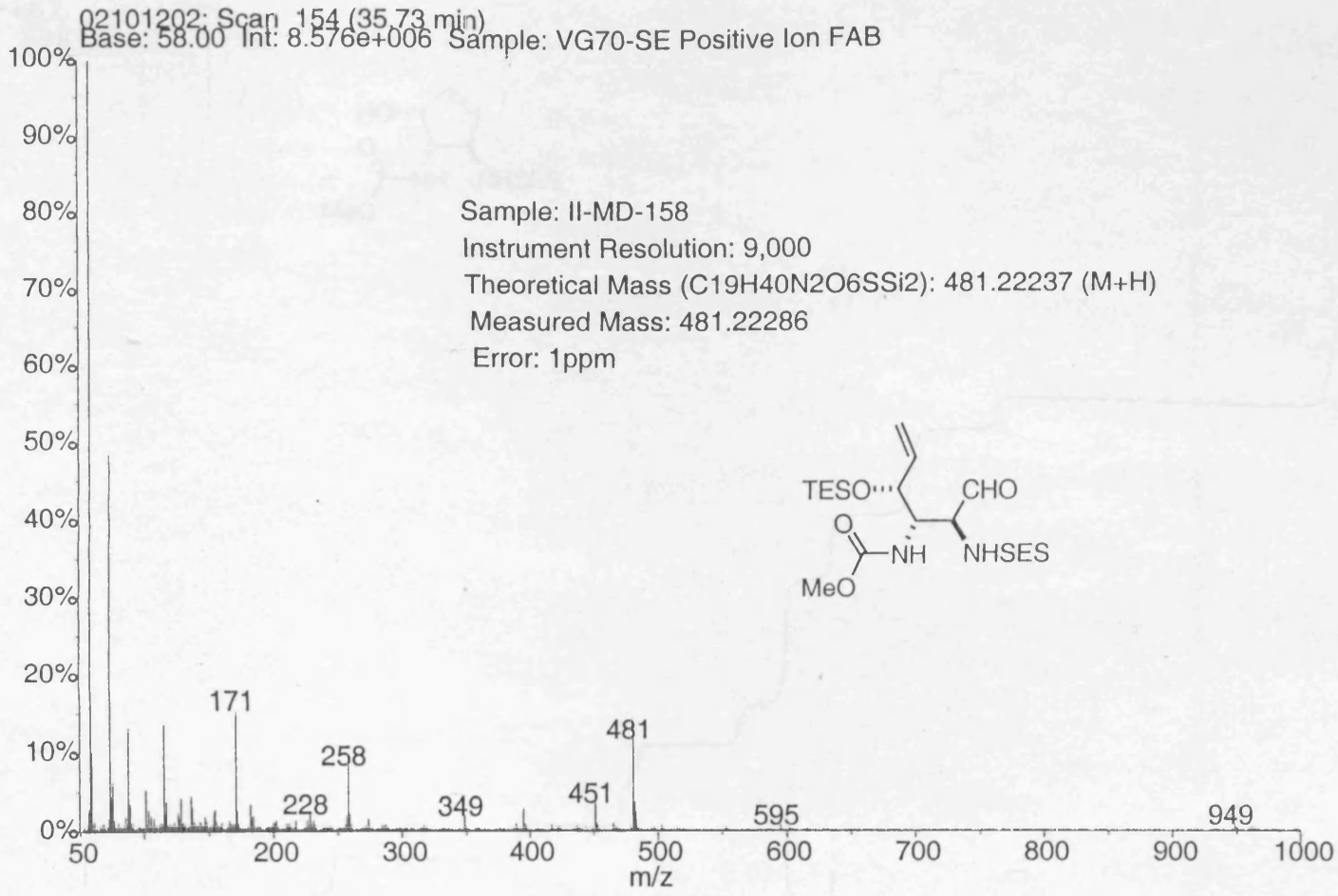




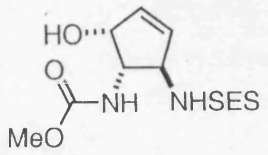
PERKIN ELMER



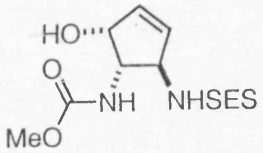
02/12/17 22:05
X: 16 scans, 16.0cm-1, apod none, flat


02101202: Scan 154 (35.73 min)
Base: 58.00 Int: 8.576e+006 Sample: VG70-SE Positive Ion FAB
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
50
200
300
400
500
600
700
800
900
1000
m/z
171
258
228
349
451
481
595
949
Sample: II-MD-158
Instrument Resolution: 9,000
Theoretical Mass (C19H40N2O6SSi2): 481.22237 (M+H)
Measured Mass: 481.22286
Error: 1ppm
TESO
CHO
O
NH
NHSES
MeO

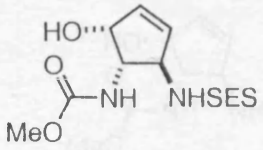
II-md-163
DMSO-d6, 298 K

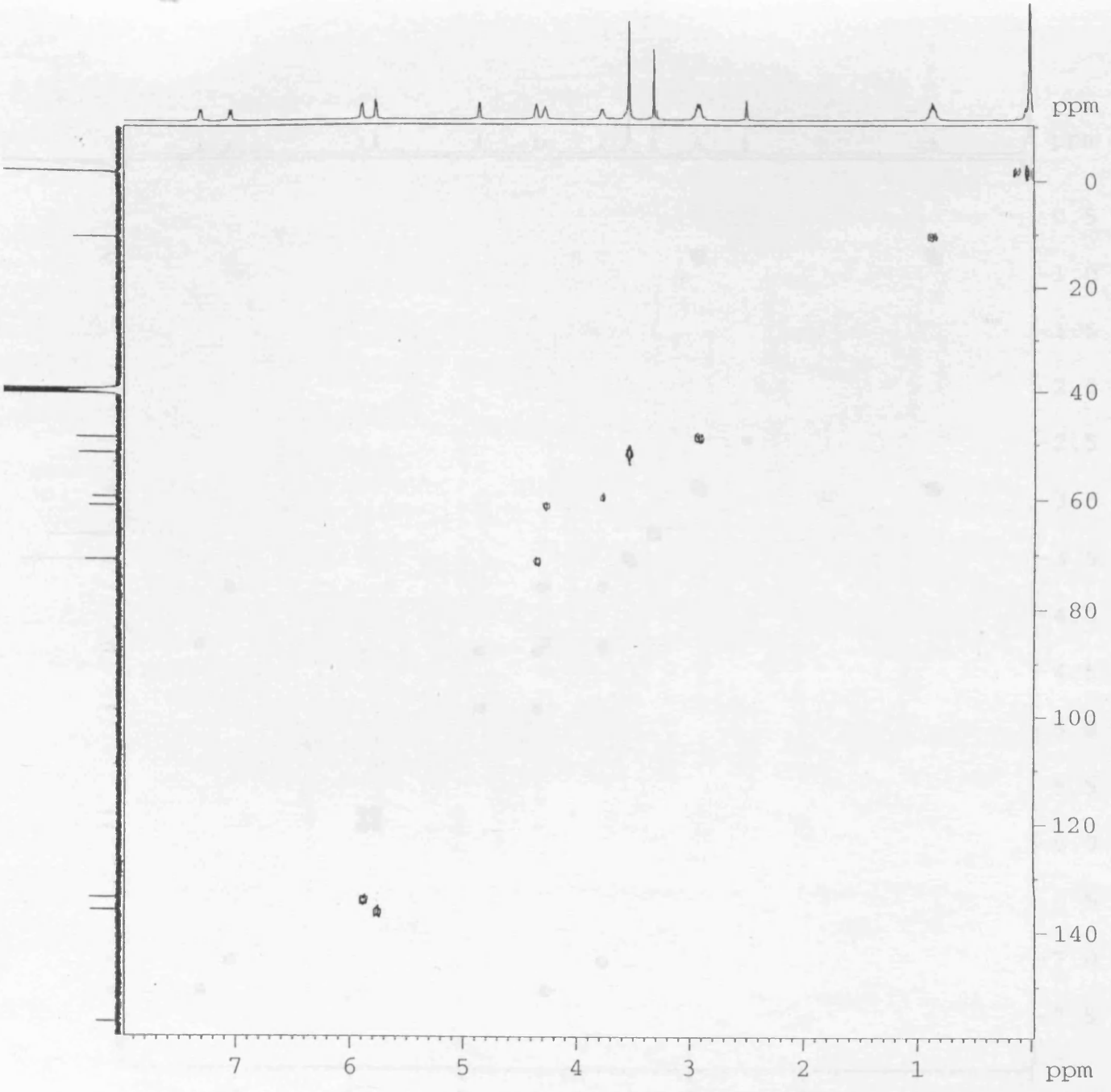


II-md-163
DMSO-d6, 298 K

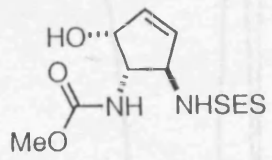


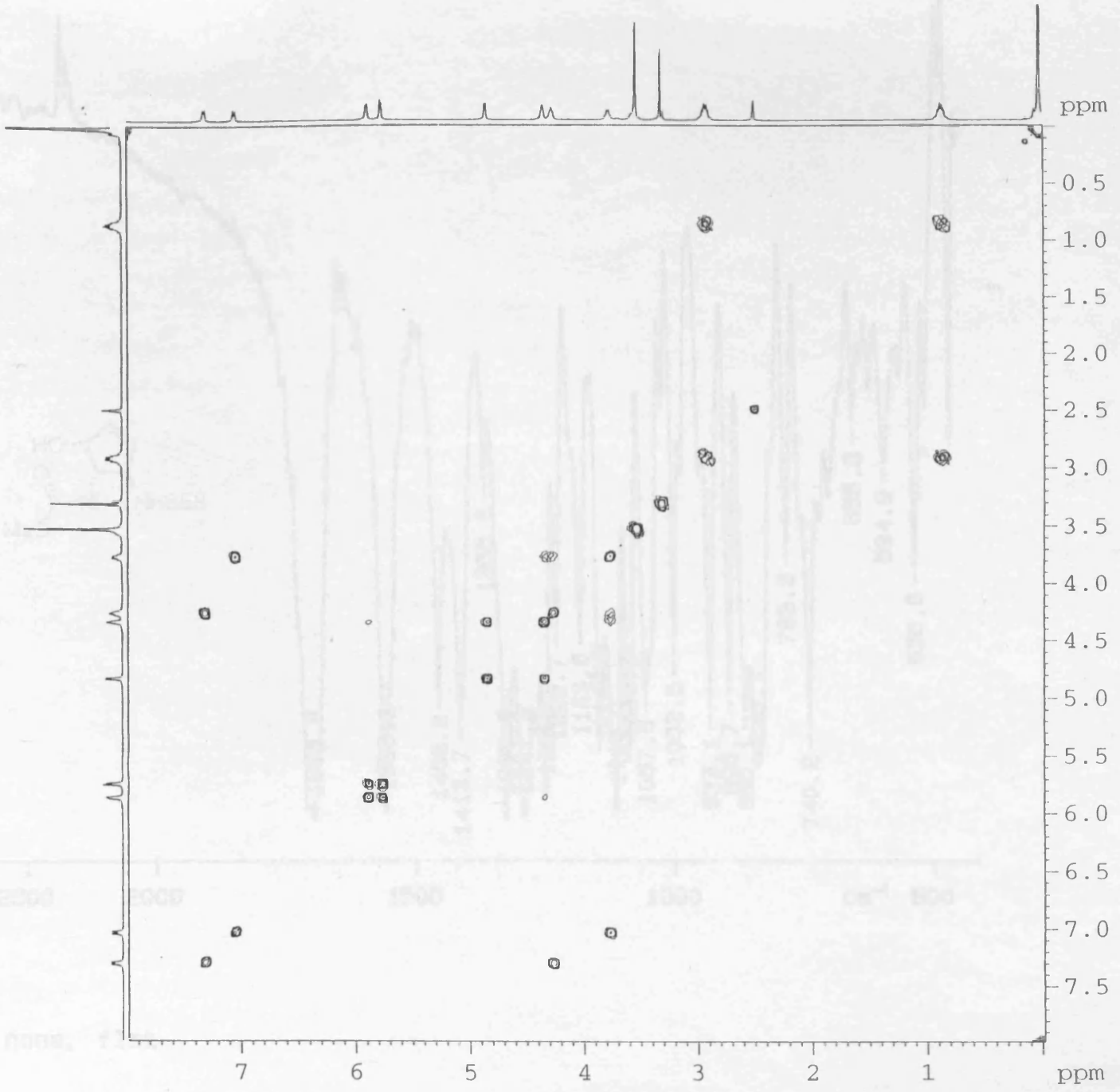
II-md-163
DMSO-d6, 298 K
HMQC



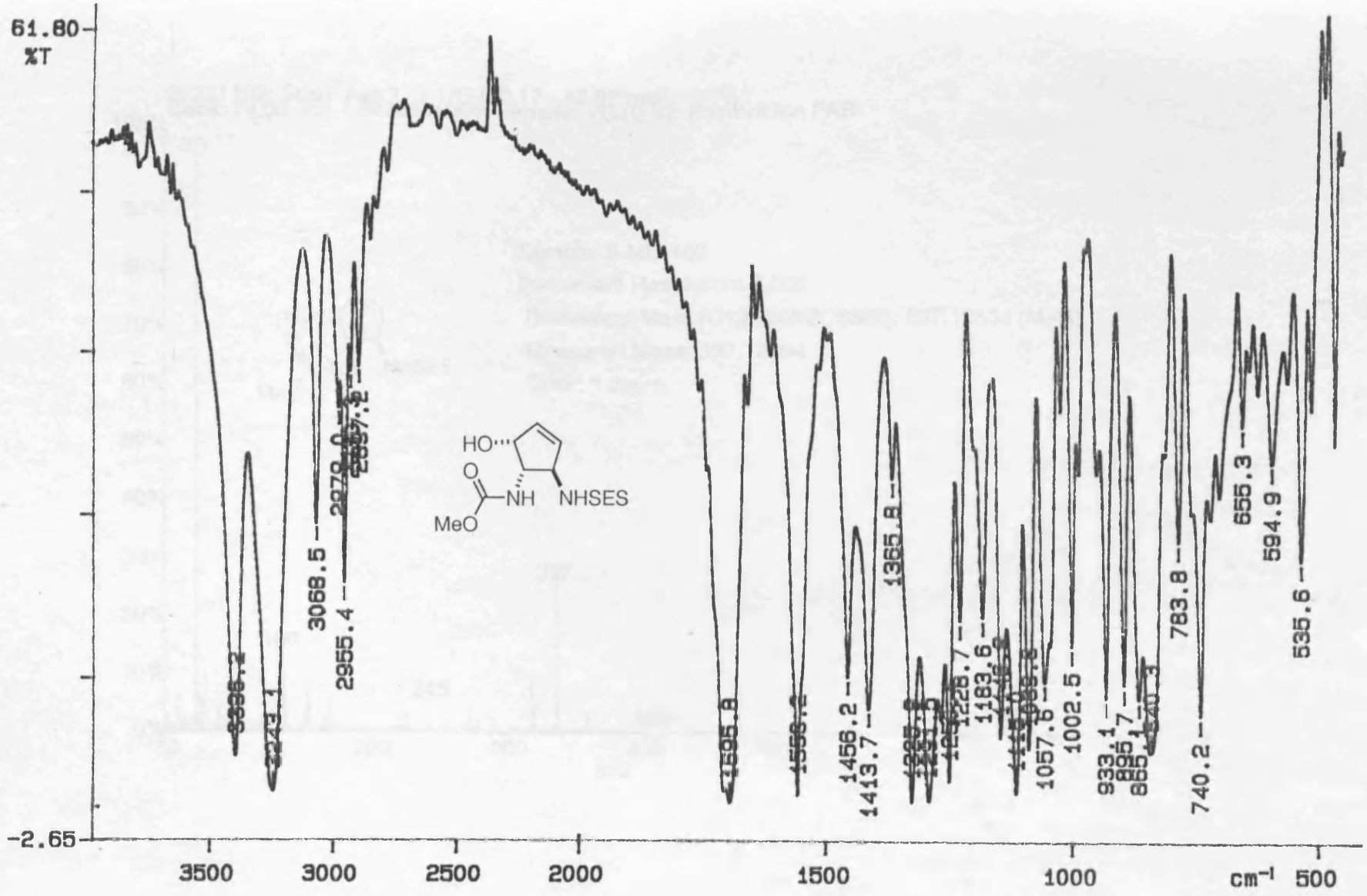


II-md-163
DMSO-d6, 298K
COSY

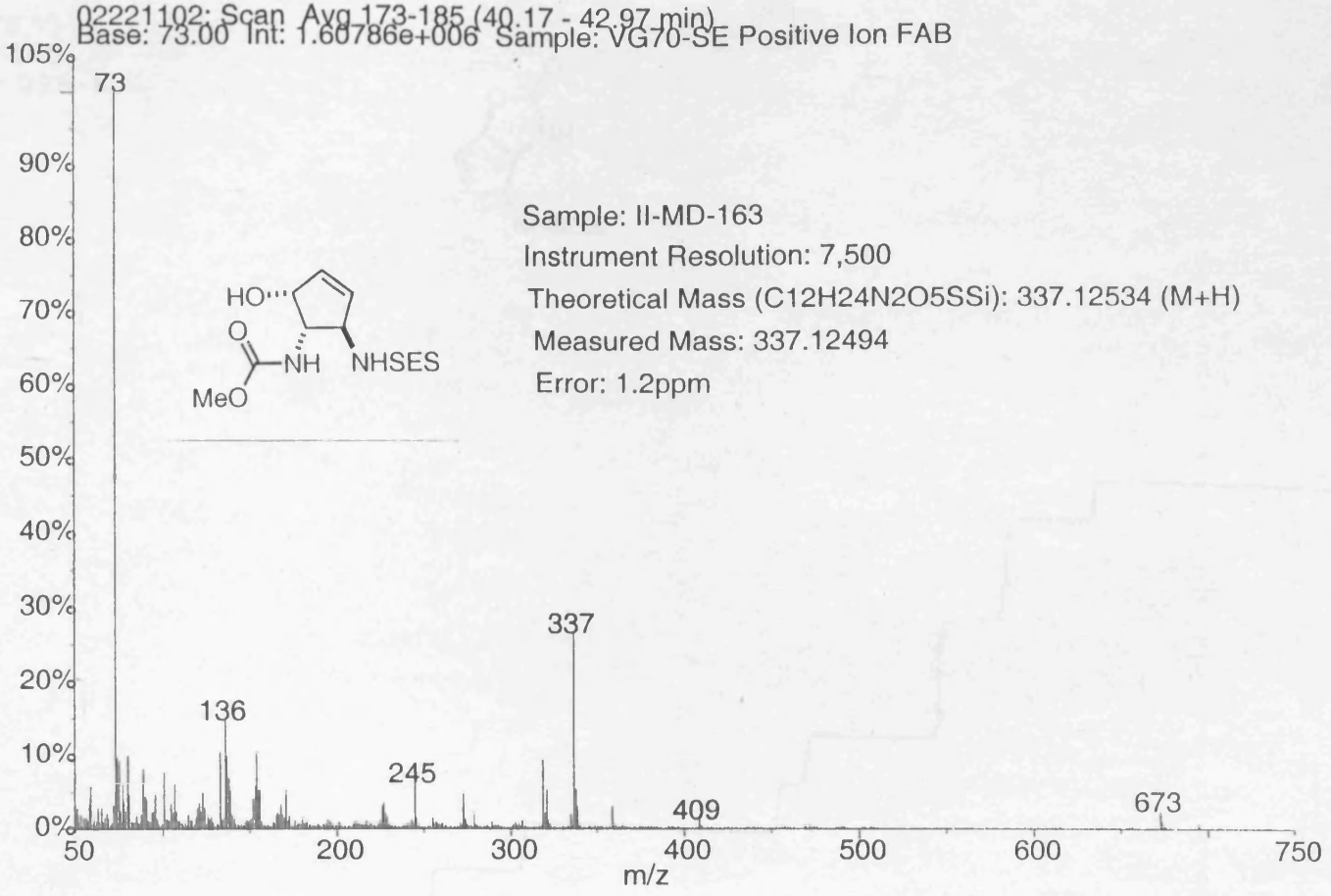




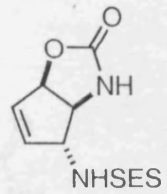
PERKIN ELMER



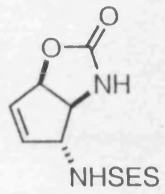
02/10/29 10:50
X: 16 scans, 16.0cm-1, apod none, flat


02221102: Scan Avg 173-185 (40.17 - 42.97 min)
Base: 73.00 Int: 1.60786e+006 Sample: VG70-SE Positive Ion FAB
105%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
73
337
136
245
409
673
50
200
300
400
500
600
750
m/z
HO
O
NH
NHSES
MeO
Sample: II-MD-163
Instrument Resolution: 7,500
Theoretical Mass (C12H24N2O5SSi): 337.12534 (M+H)
Measured Mass: 337.12494
Error: 1.2ppm

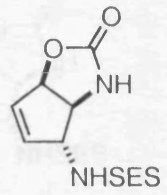
II-md-165
DMSO-d6, 298 K

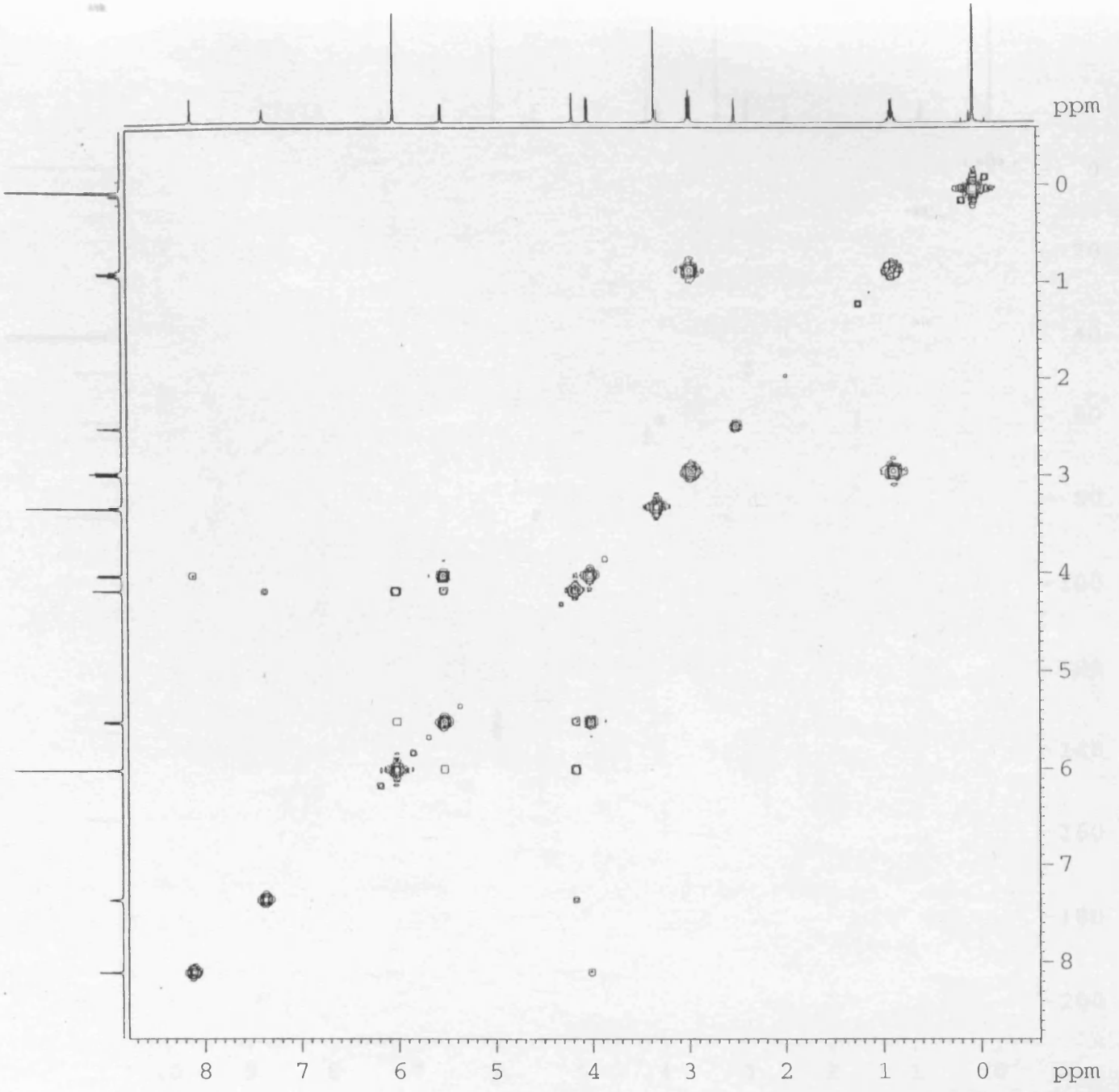


II-md-165
DMSO-d6, 298 K

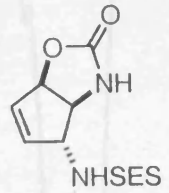


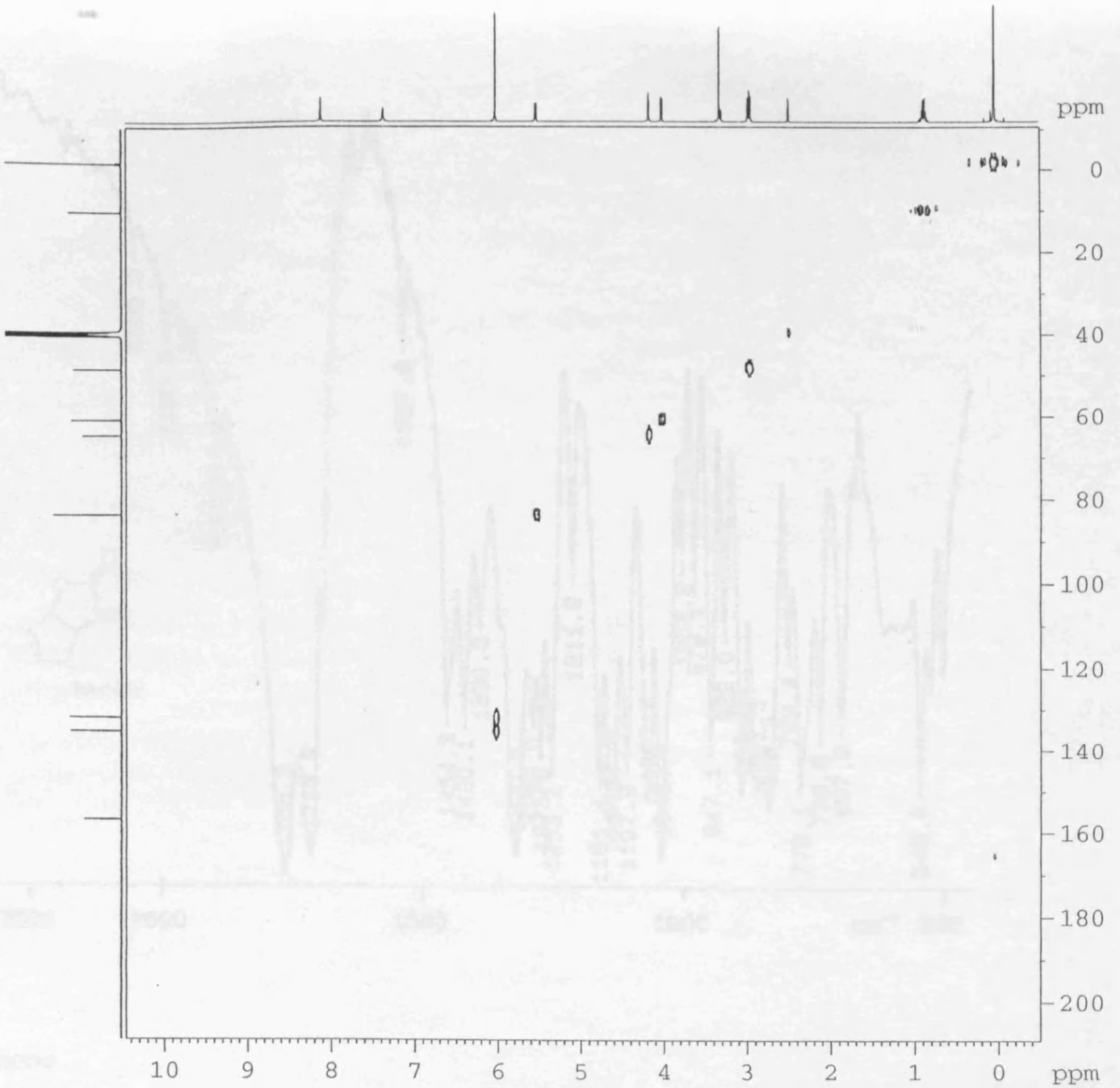
II-md-165
DMSO-d6, 298 K
COSY



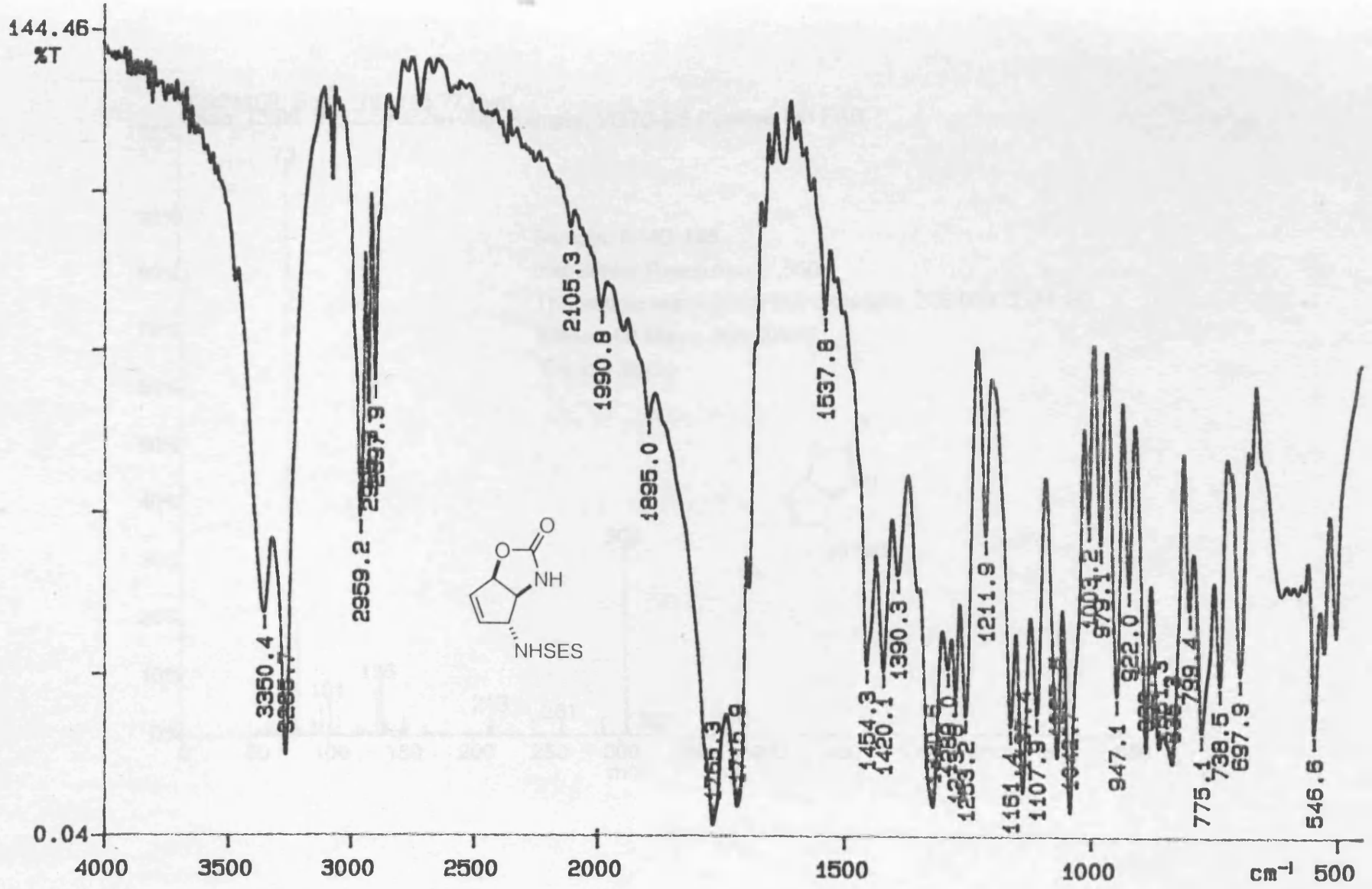


II-md-165
DMSO-d6, 298 K
HMQC

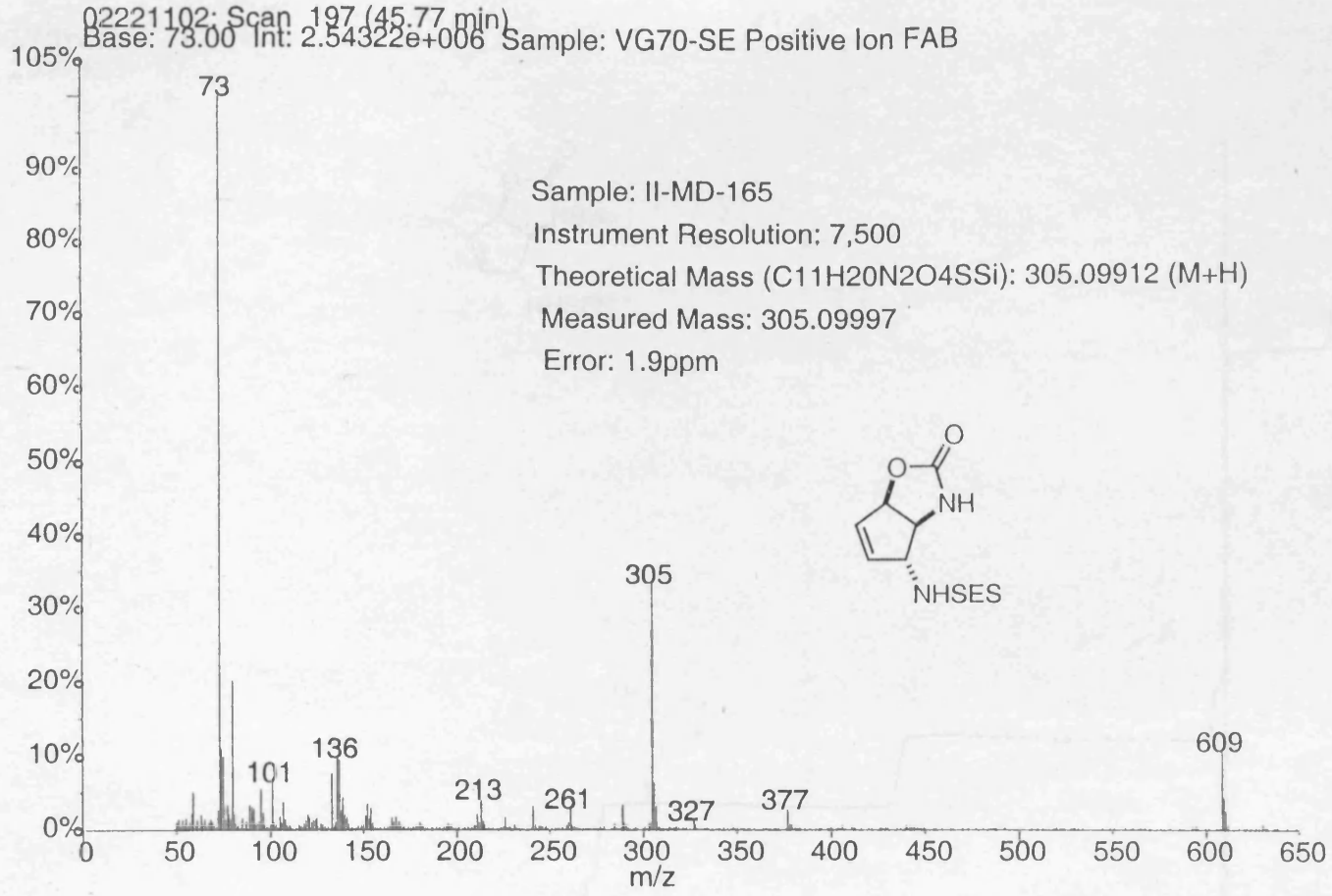




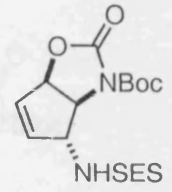
PERKIN ELMER



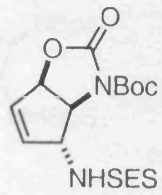
02/10/30 15:20
X: 64 scans, 16.0cm-1, apod none


02221102: Scan 197 (45.77 min)
Base: 73.00 Int: 2.54322e+006 Sample: VG70-SE Positive Ion FAB
Sample: II-MD-165
Instrument Resolution: 7,500
Theoretical Mass (C11H20N2O4SSi): 305.09912 (M+H)
Measured Mass: 305.09997
Error: 1.9ppm
O
O
NH
NHSES
105%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
73
305
136
101
213
261
327
377
609
0
50
100
150
200
250
300
350
400
450
500
550
600
650
m/z

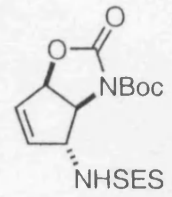
II-md-170b
CDCl3, 298 K

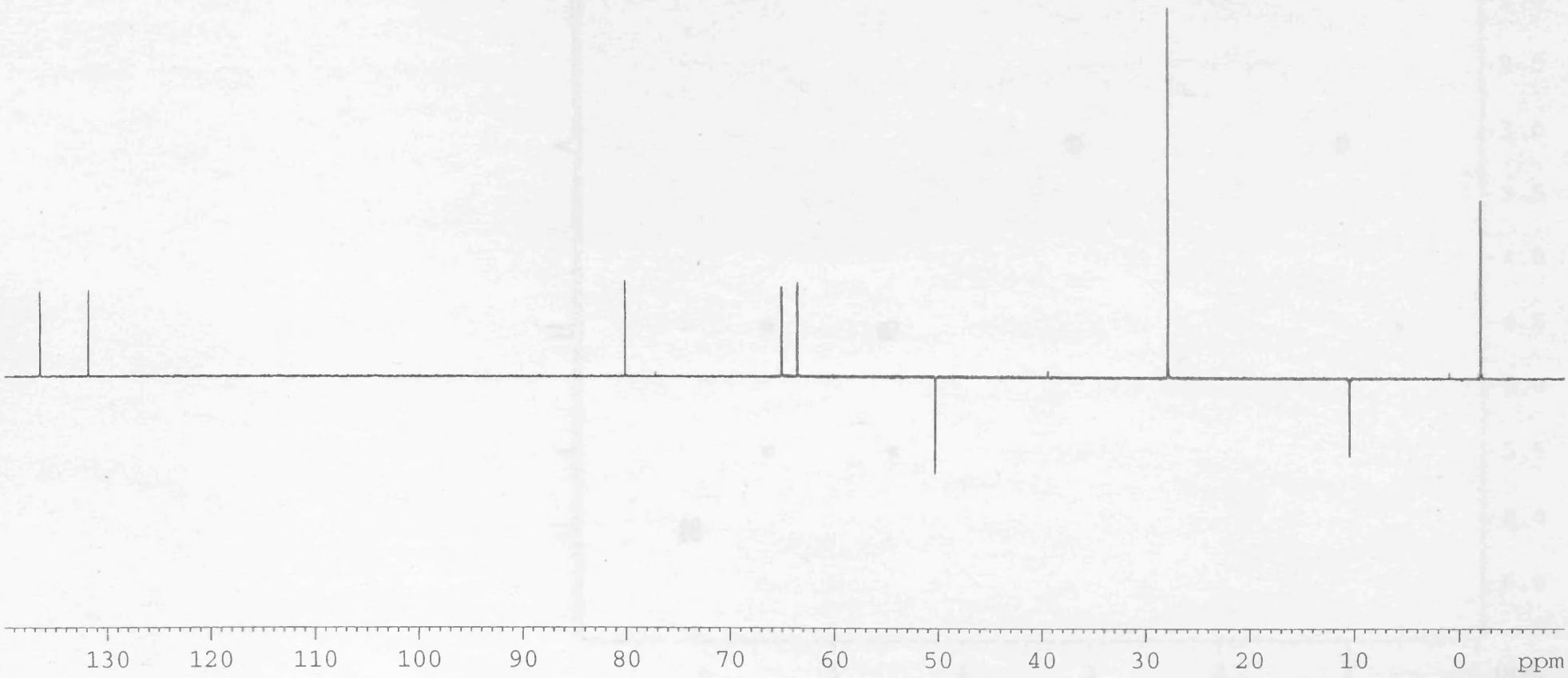


II-md-170B
CDCl3, 298 K

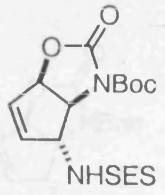


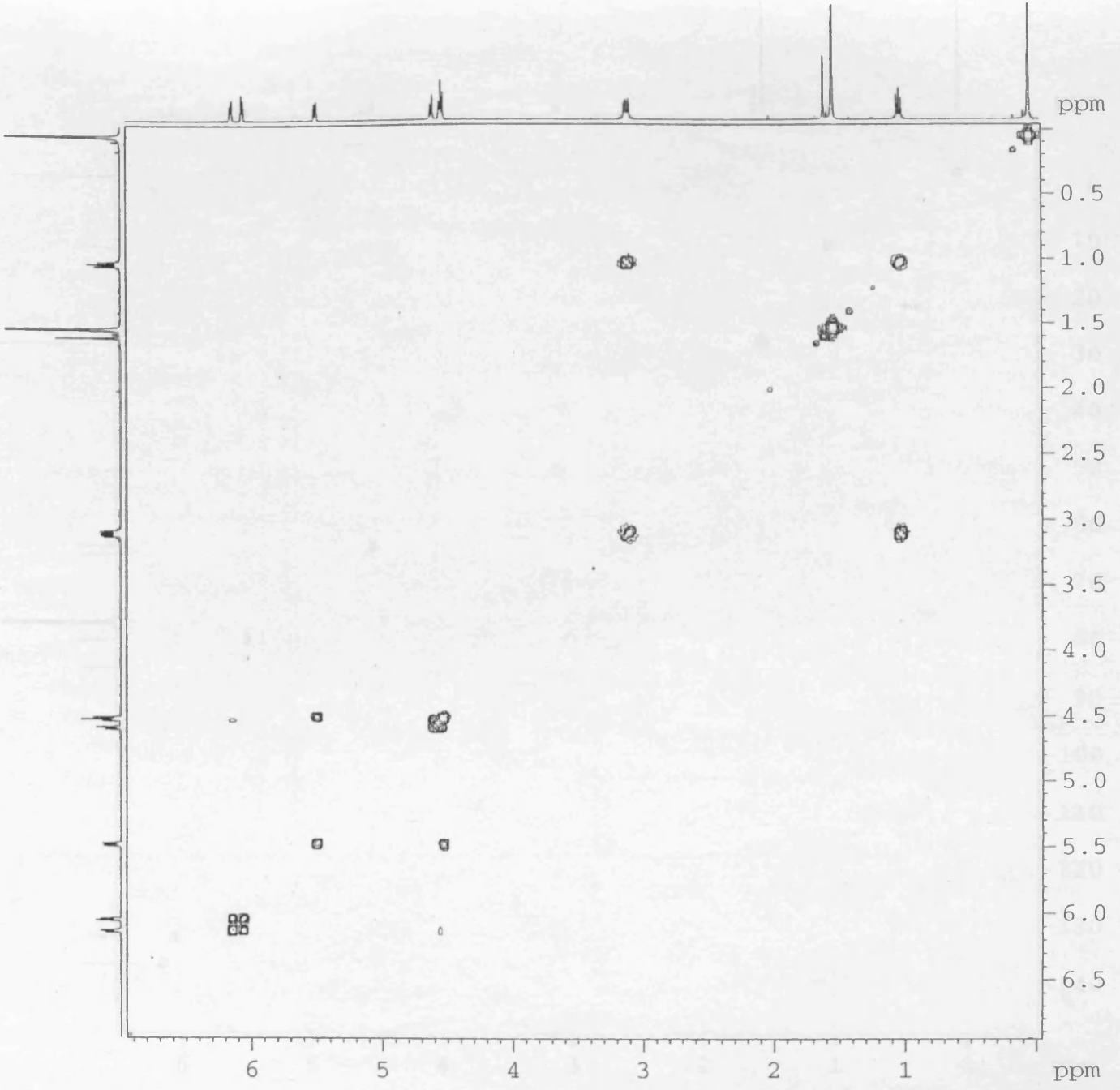
II-md-170b
CDCl3, 298 k
DEPT



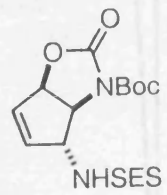


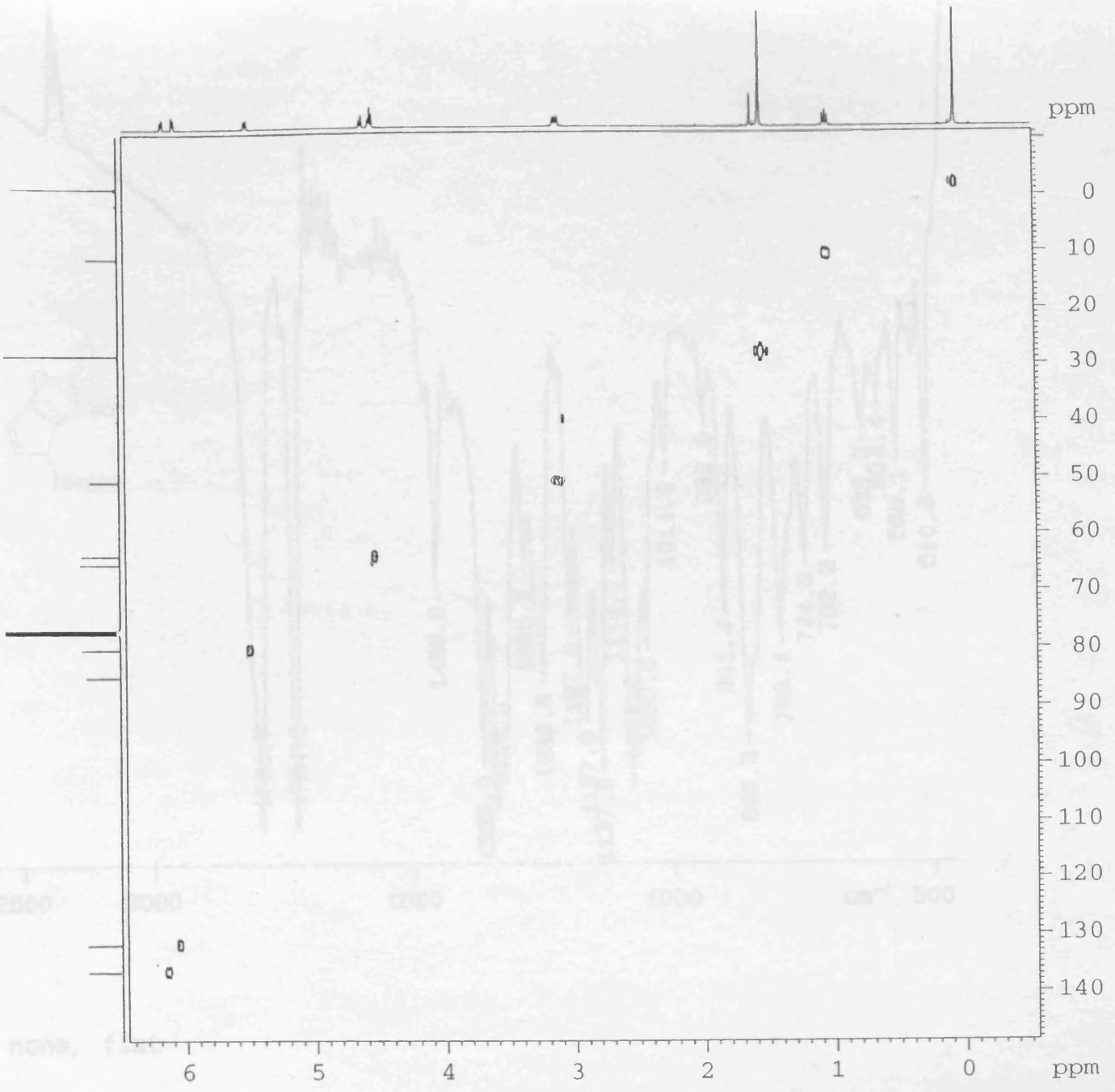
II-md-170b
CDCl3, 298 K
COSY

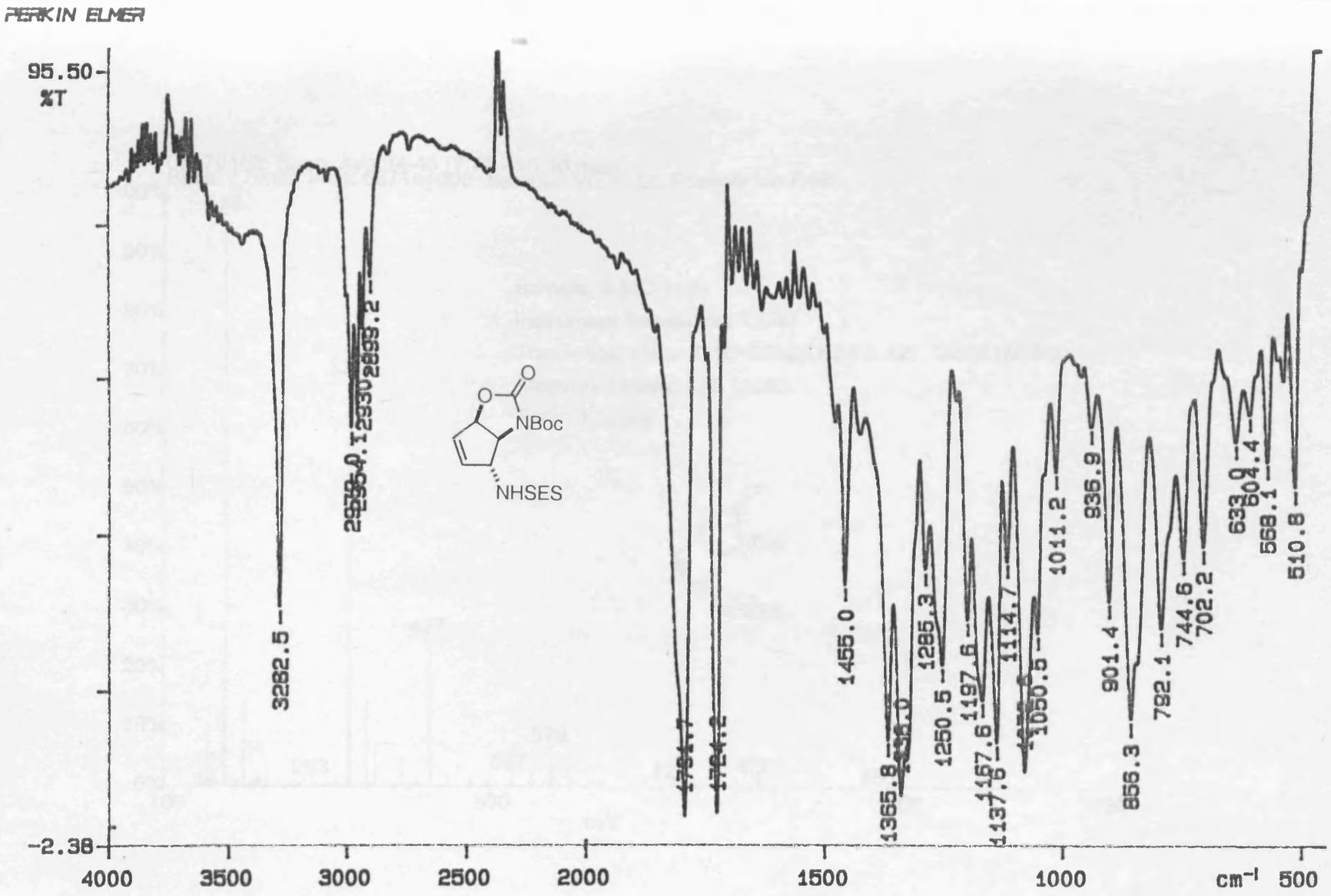


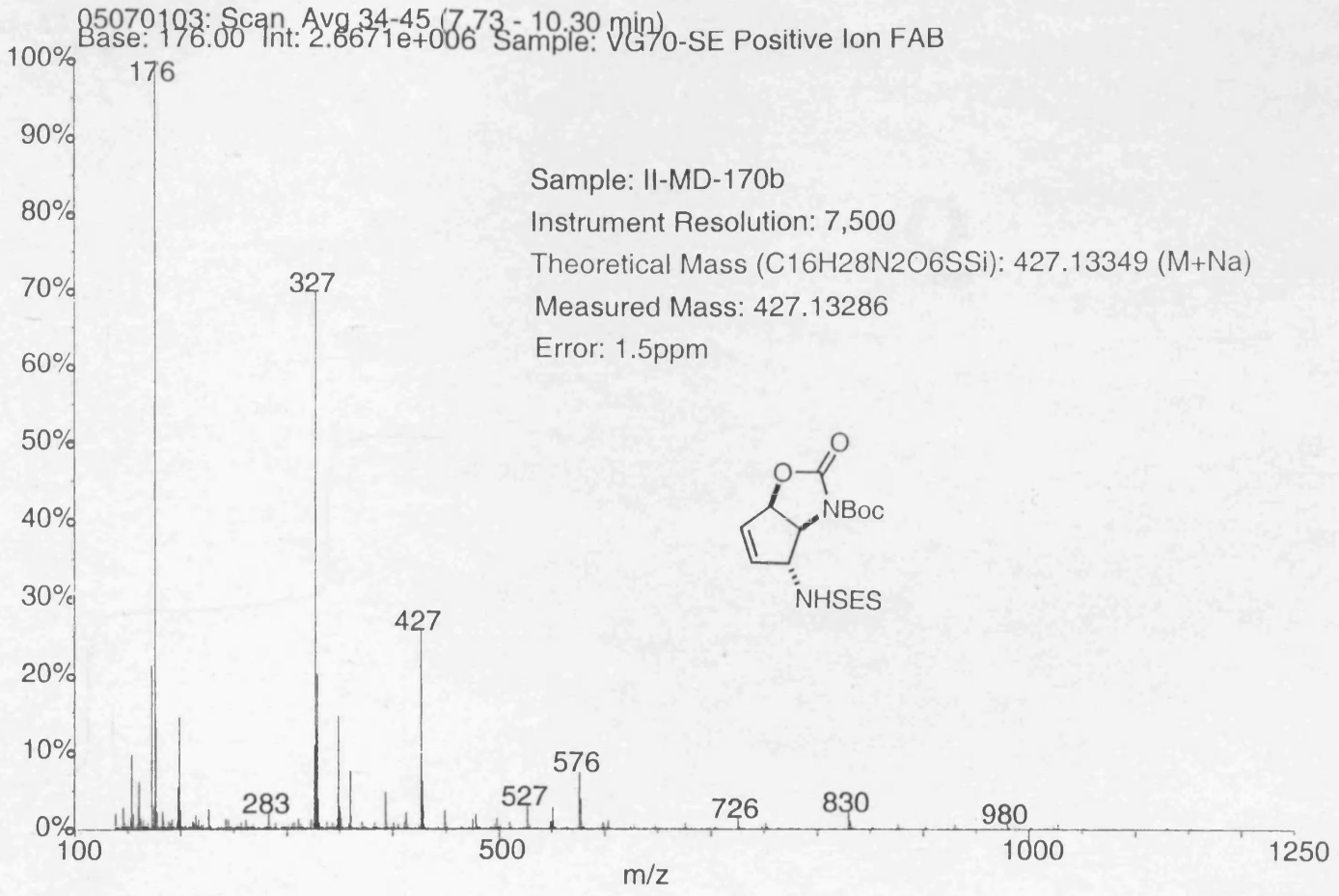


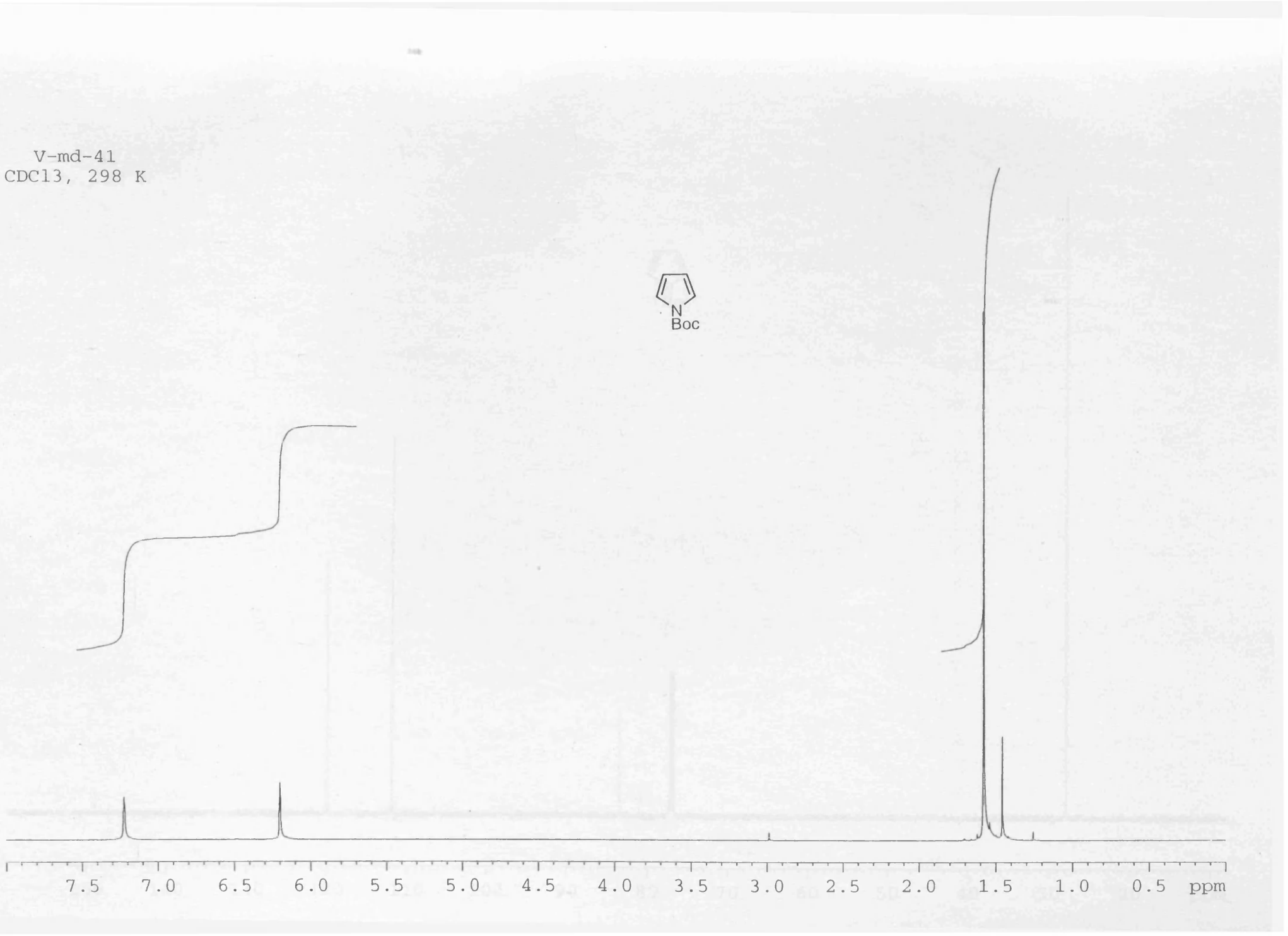
II-md-170b
CDCl3, 298 K
HMQC



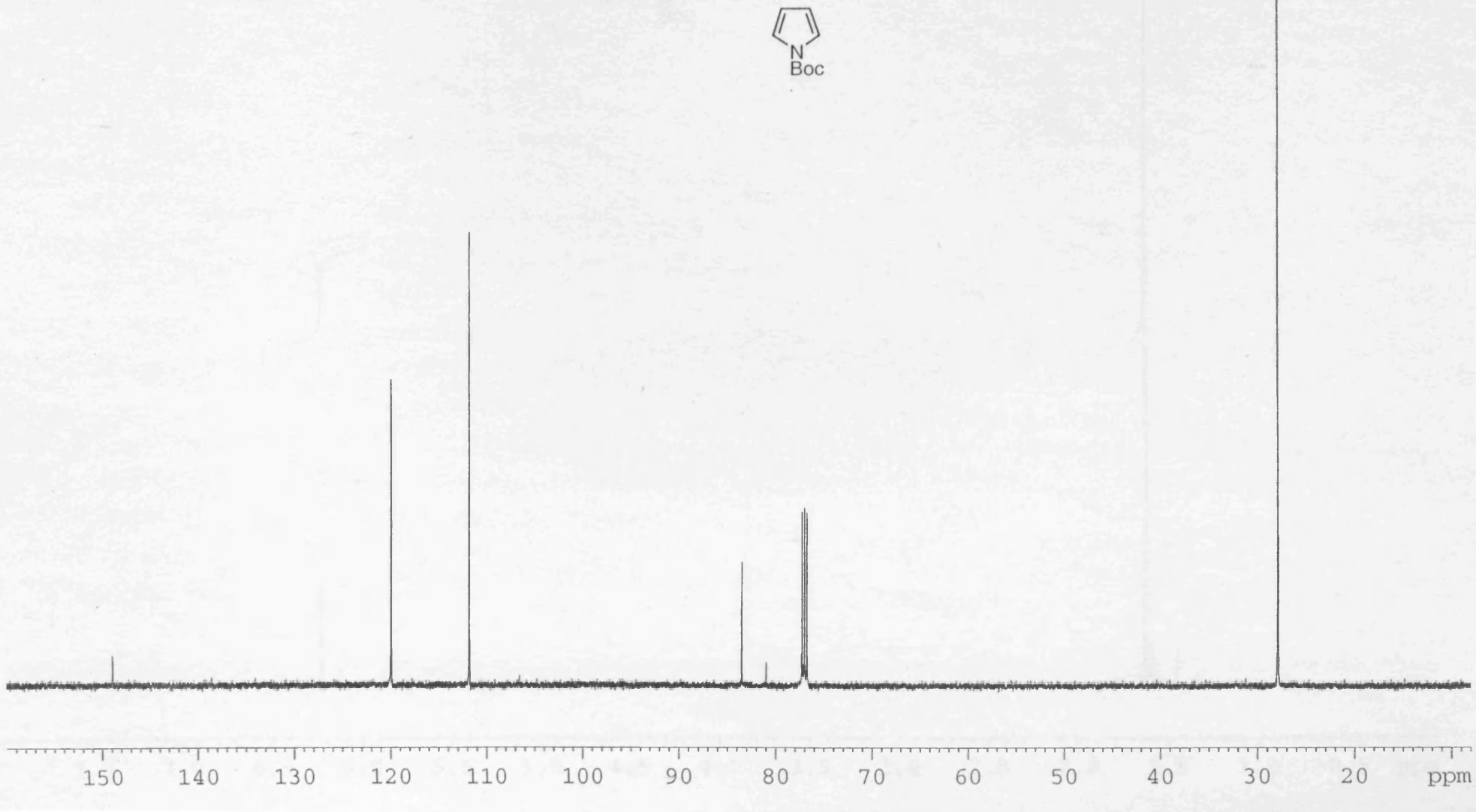



PERKIN ELMER
95.50
%T
-2.38
4000
3500
3000
2500
2000
1500
1000
cm-1
500
3282.5
2930.1
2893.2
1455.0
1365.8
1285.3
1250.5
1197.6
1167.6
1137.5
1114.7
1050.5
1011.2
936.9
901.4
856.3
792.1
744.6
702.2
633.9
604.4
568.1
510.8
NBoc
NHSES
02/11/05 12:07
X: 256 scans, 16.0cm-1, apod none, flat

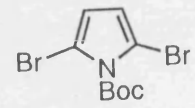

05070103: Scan Avg 34-45 (7.73 - 10.30 min)
Base: 176.00 Int: 2.6671e+006 Sample: VG70-SE Positive Ion FAB
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
176
327
427
283
527
576
726
830
980
100
500
1000
1250
m/z
Sample: II-MD-170b
Instrument Resolution: 7,500
Theoretical Mass (C16H28N2O6SSi): 427.13349 (M+Na)
Measured Mass: 427.13286
Error: 1.5ppm
O
O
NBoc
NHSES


V-md-41
CDC13, 298 K
N
Boc
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

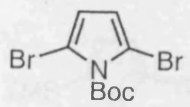
V-md-41
CDCl3, 298 K



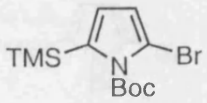
V-md-42
CDCl3, 298 K



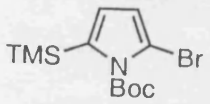
V-md-42
CDCl3, 298 K

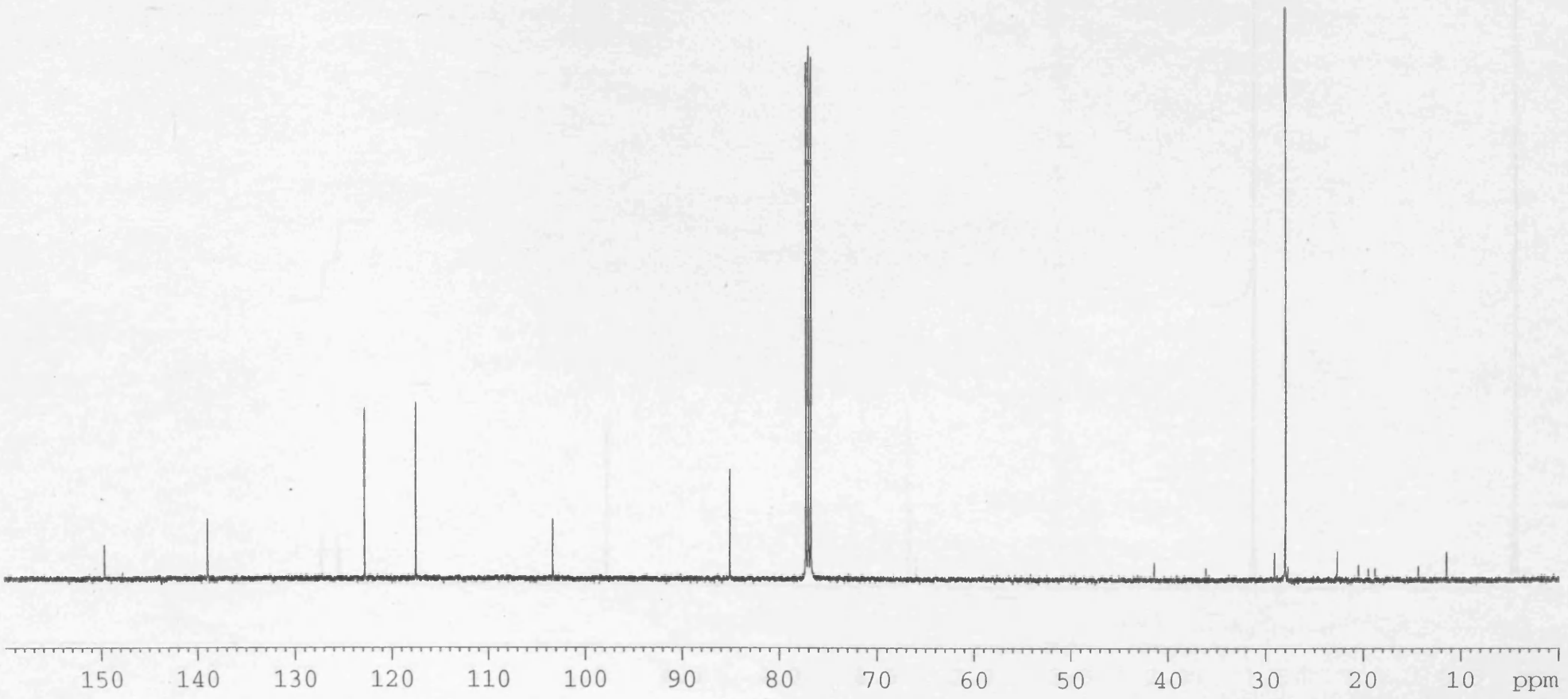


V-md-44
CDCl3, 298 K

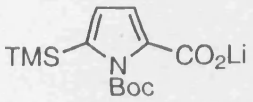


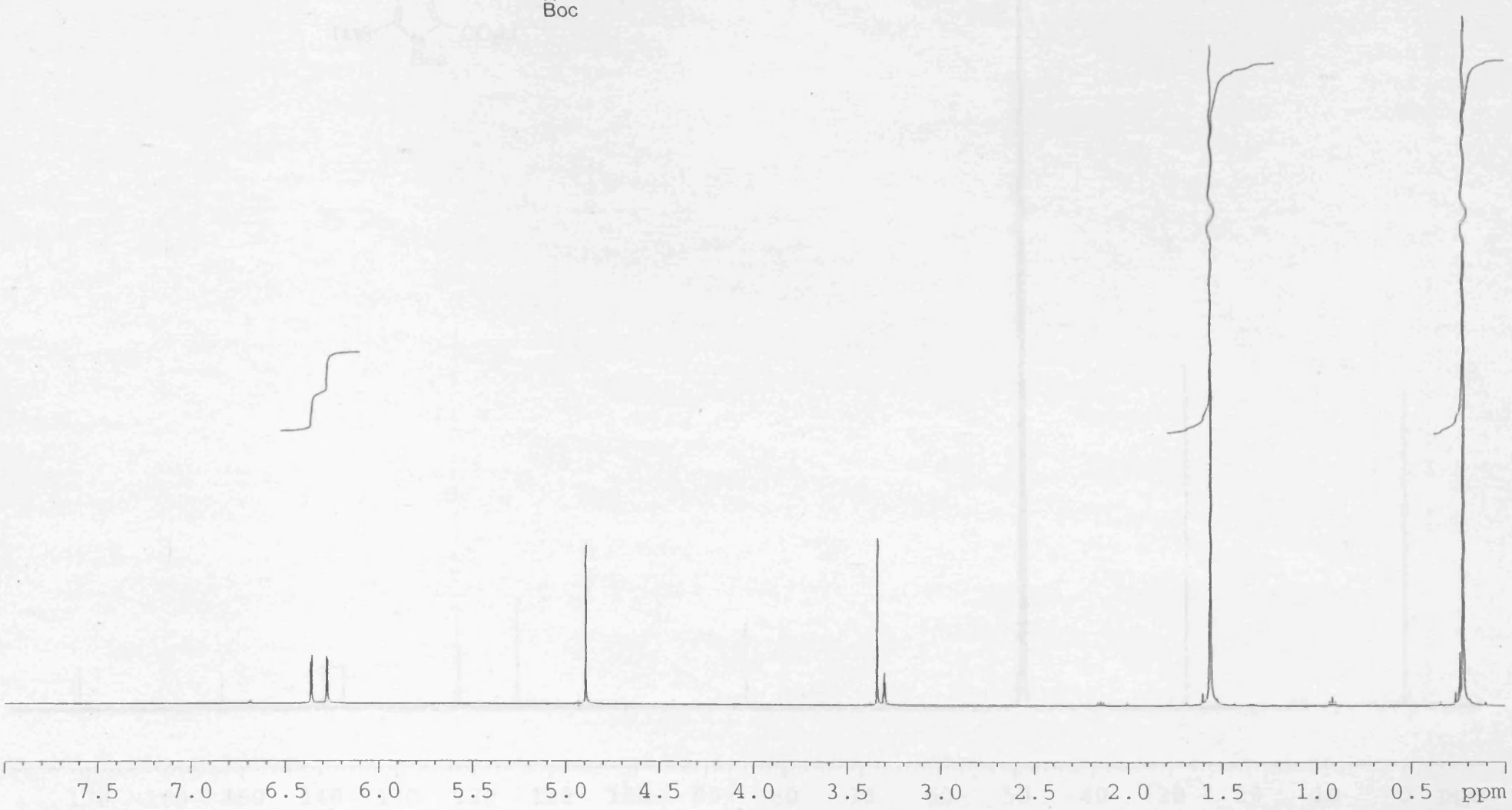
V-md-44
CDCl3, 298 K



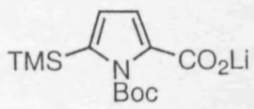


V-md-46
MeOD, 298 K

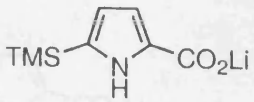




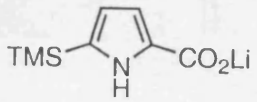
V-md-46
MeOD, 298 K

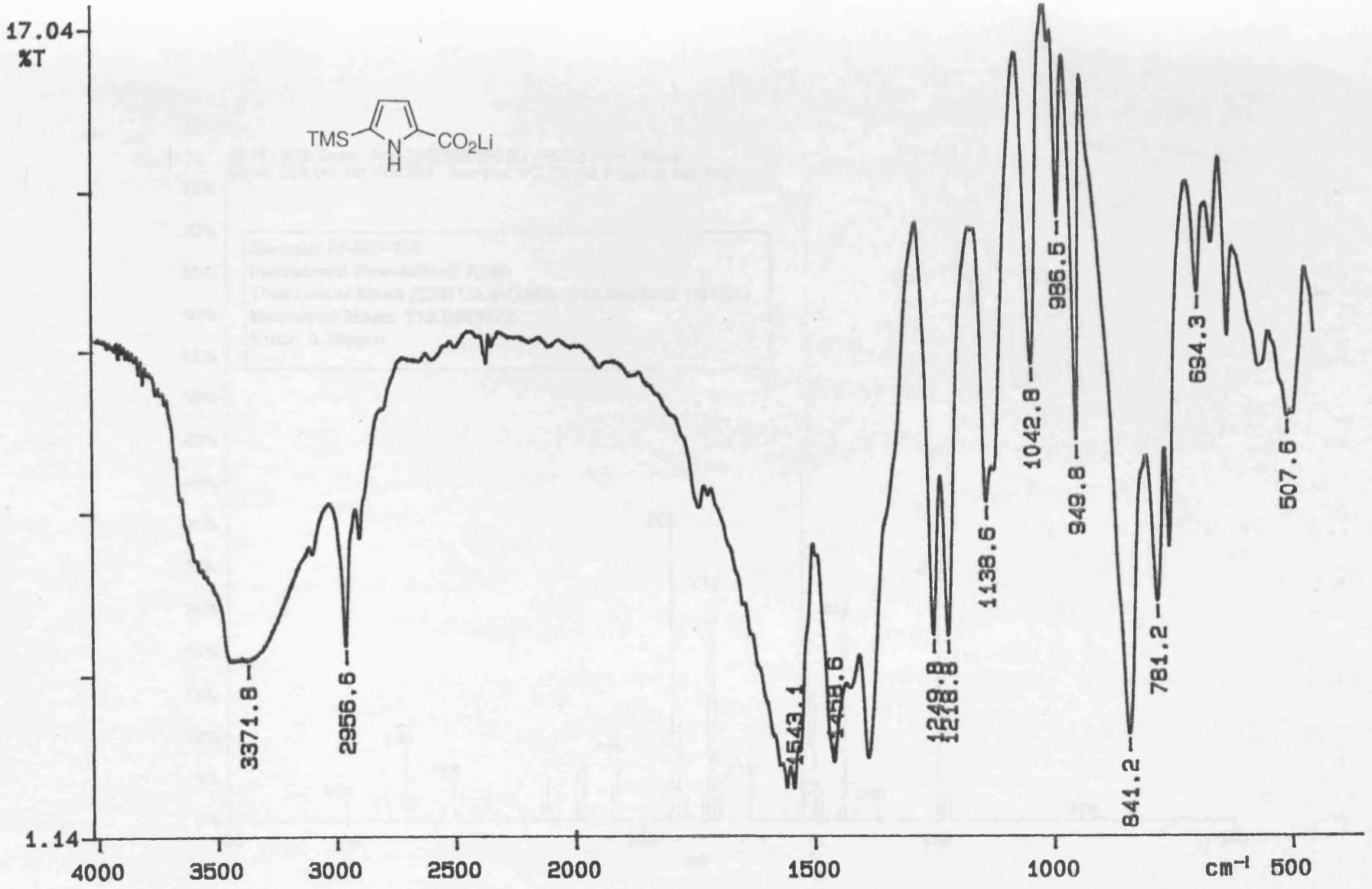


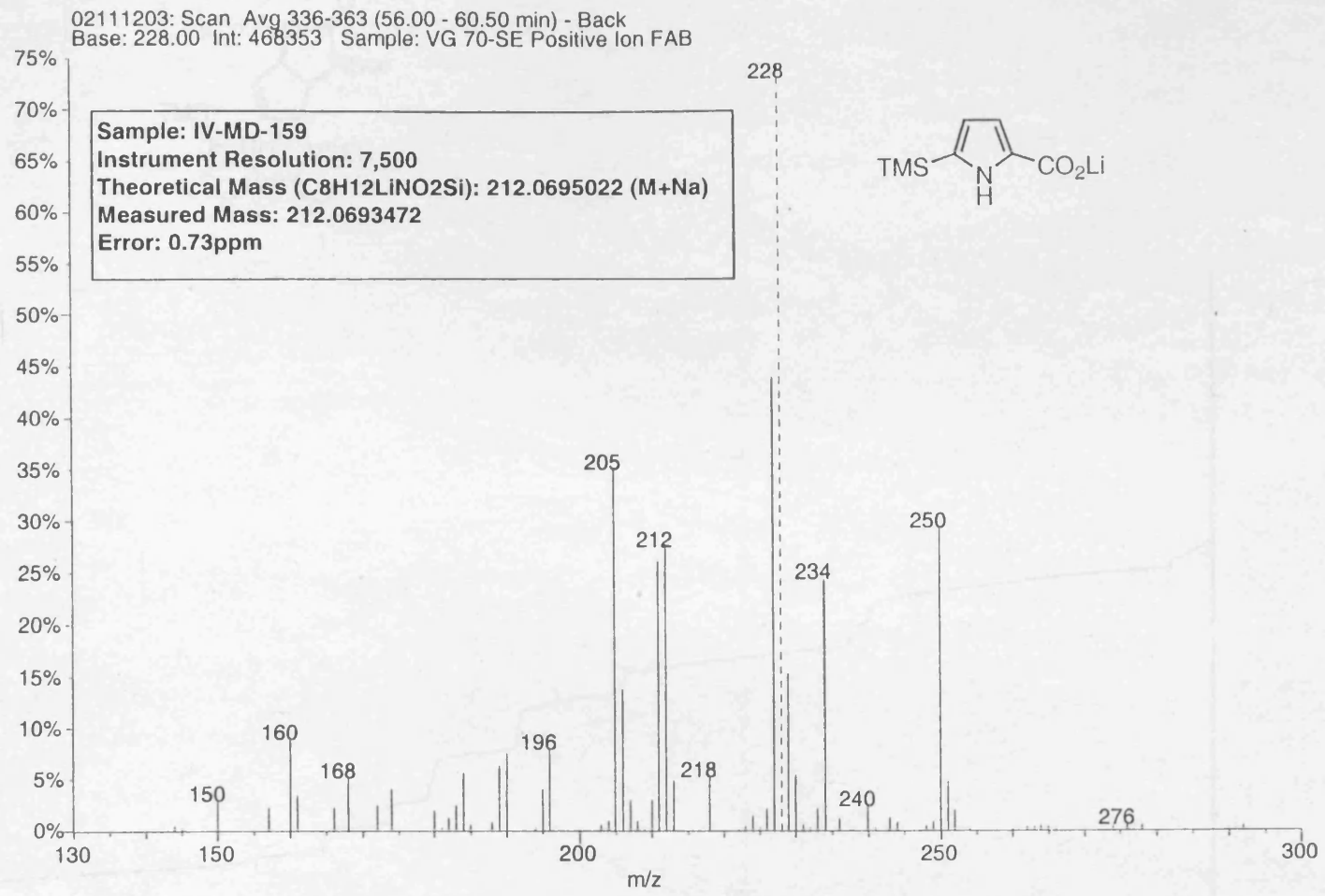
IV-md-159
MeOD, 298 K



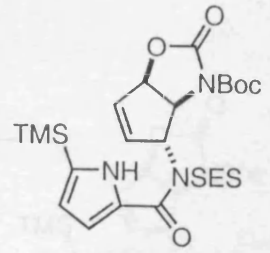
IV-md-159
MeOD, 298 K



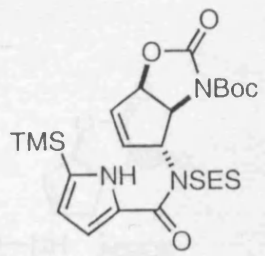

17.04
%T
TMS
N
H
CO2Li
3371.8
2956.6
1543.1
1458.6
1249.8
1218.8
1138.6
1042.8
986.5
949.8
841.2
781.2
694.3
507.6
1.14
4000
3500
3000
2500
2000
1500
1000
cm-1
500


02111203: Scan Avg 336-363 (56.00 - 60.50 min) - Back
Base: 228.00 Int: 468353 Sample: VG 70-SE Positive Ion FAB
Sample: IV-MD-159
Instrument Resolution: 7,500
Theoretical Mass (C8H12LiNO2Si): 212.0695022 (M+Na)
Measured Mass: 212.0693472
Error: 0.73ppm
TMS
N
H
CO2Li
75%
70%
65%
60%
55%
50%
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
130
150
200
250
300
m/z
228
205
212
234
250
160
196
168
218
150
240
276

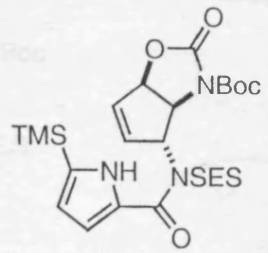
III-md-83
CDCl3, 298 K

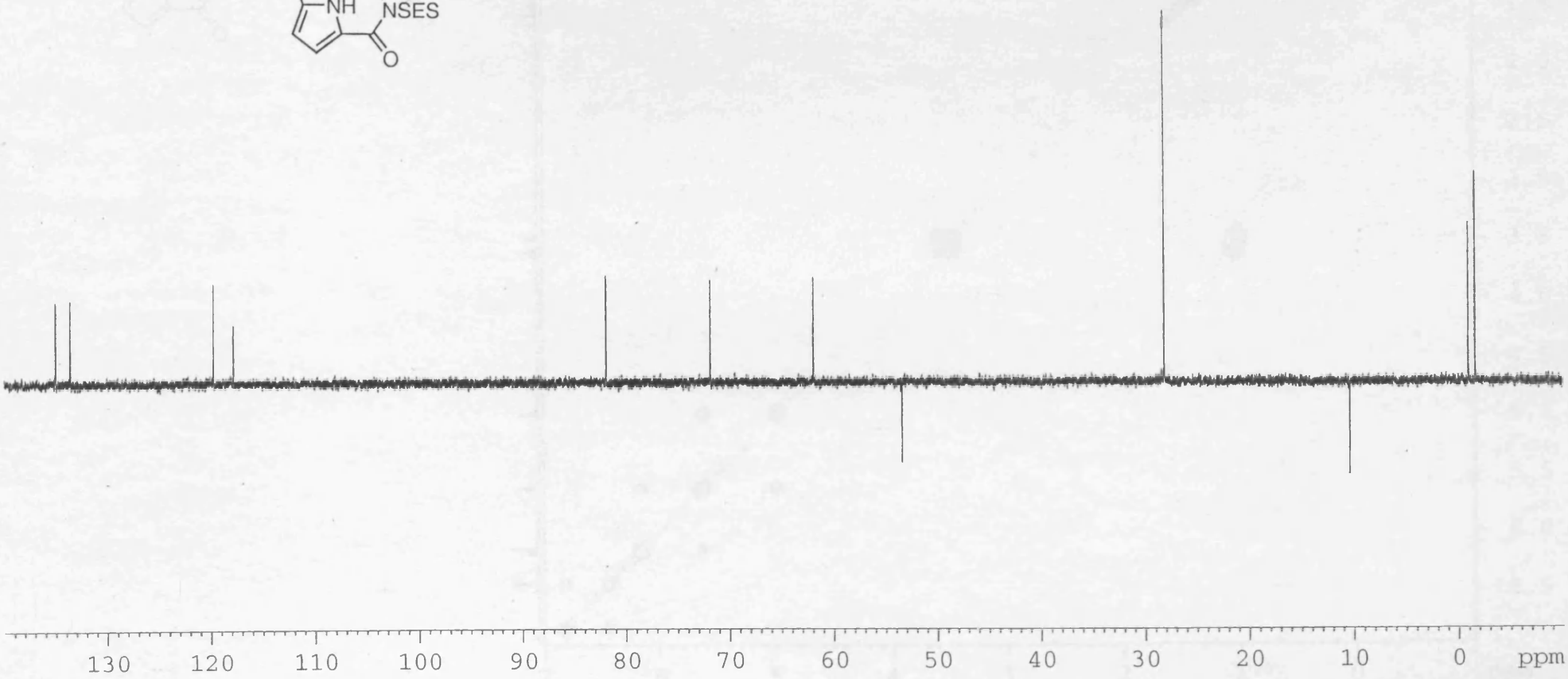


III-md-83
CDCl3, 298 K

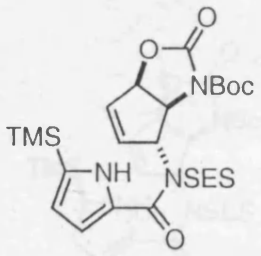


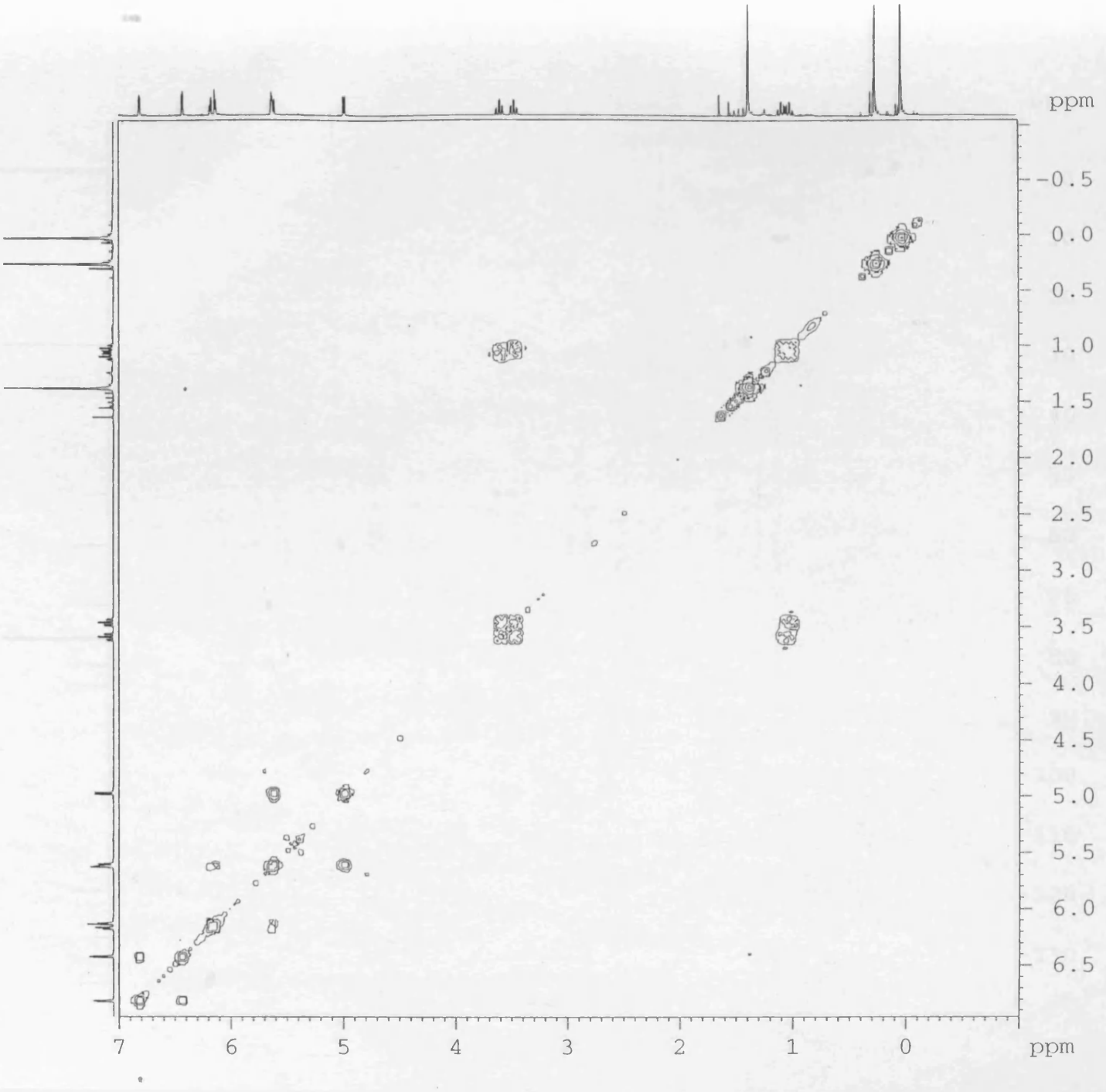
III-md-83
CDCl3, 298 K
DEPT



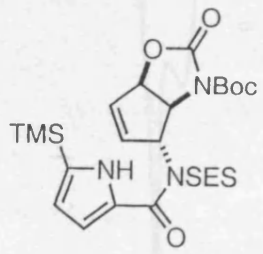


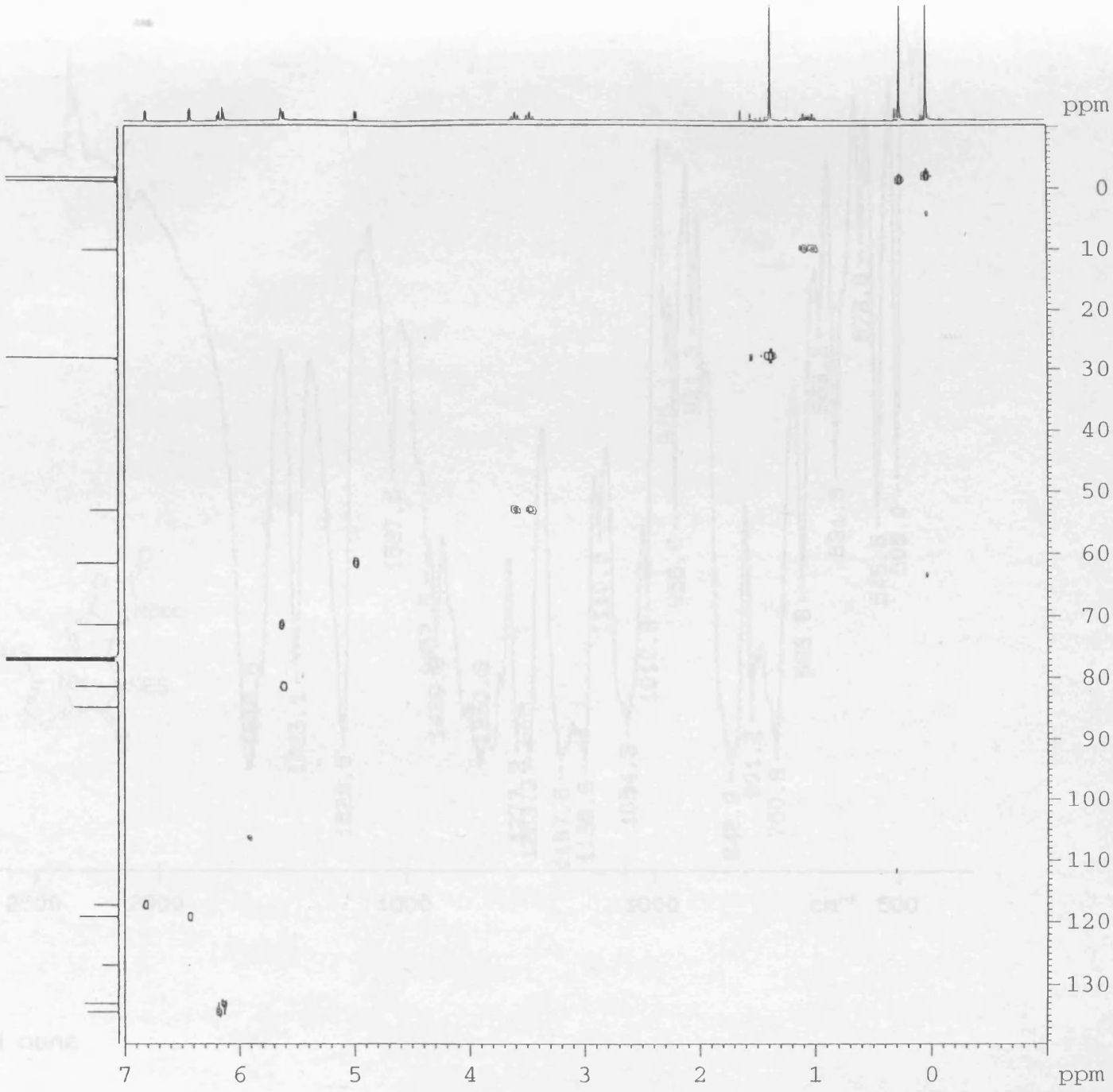
III-md-83
CDCl3, 298 K
COSY



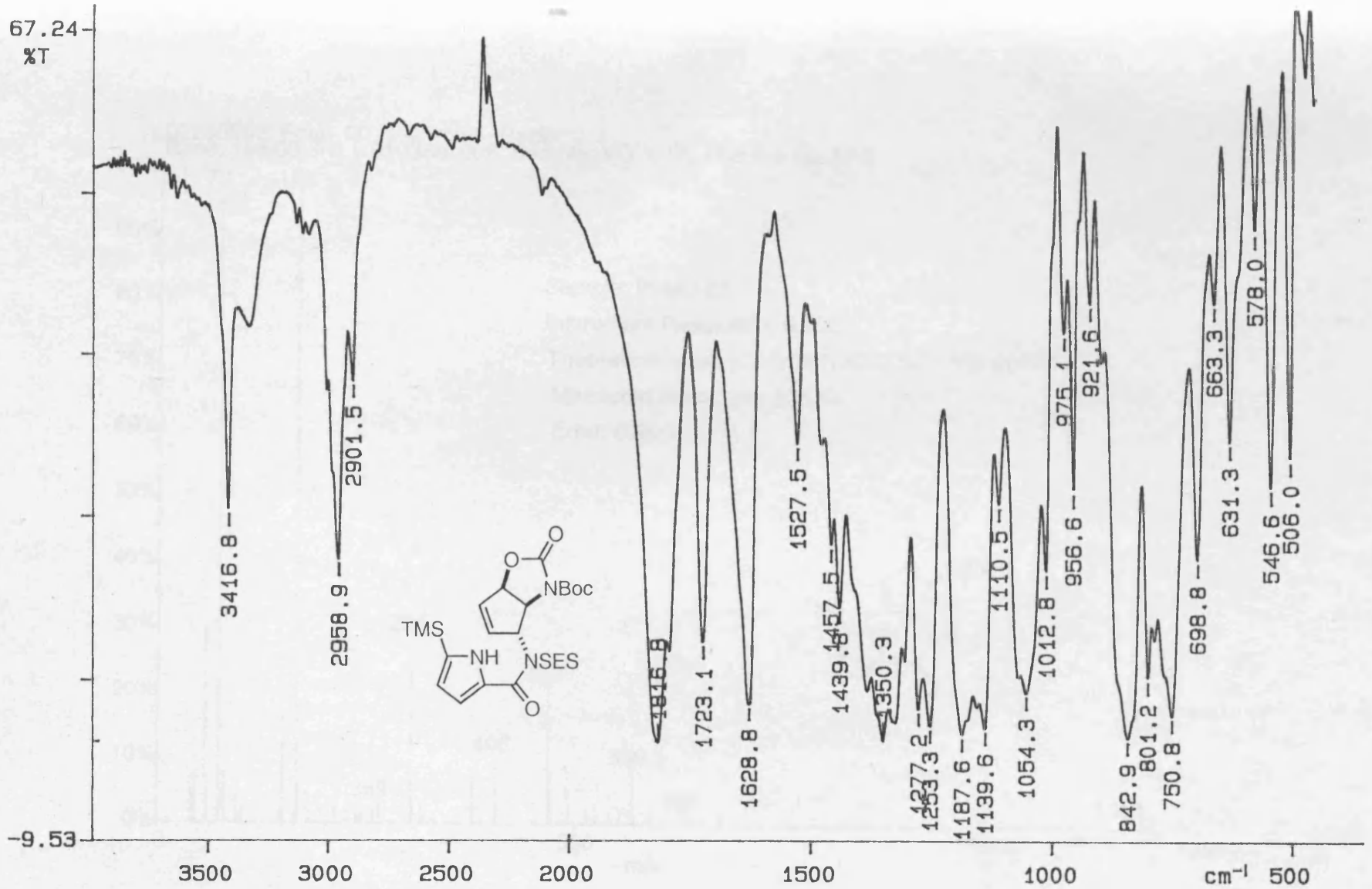


III-md-83
CDCl3, 298 K
HMQC

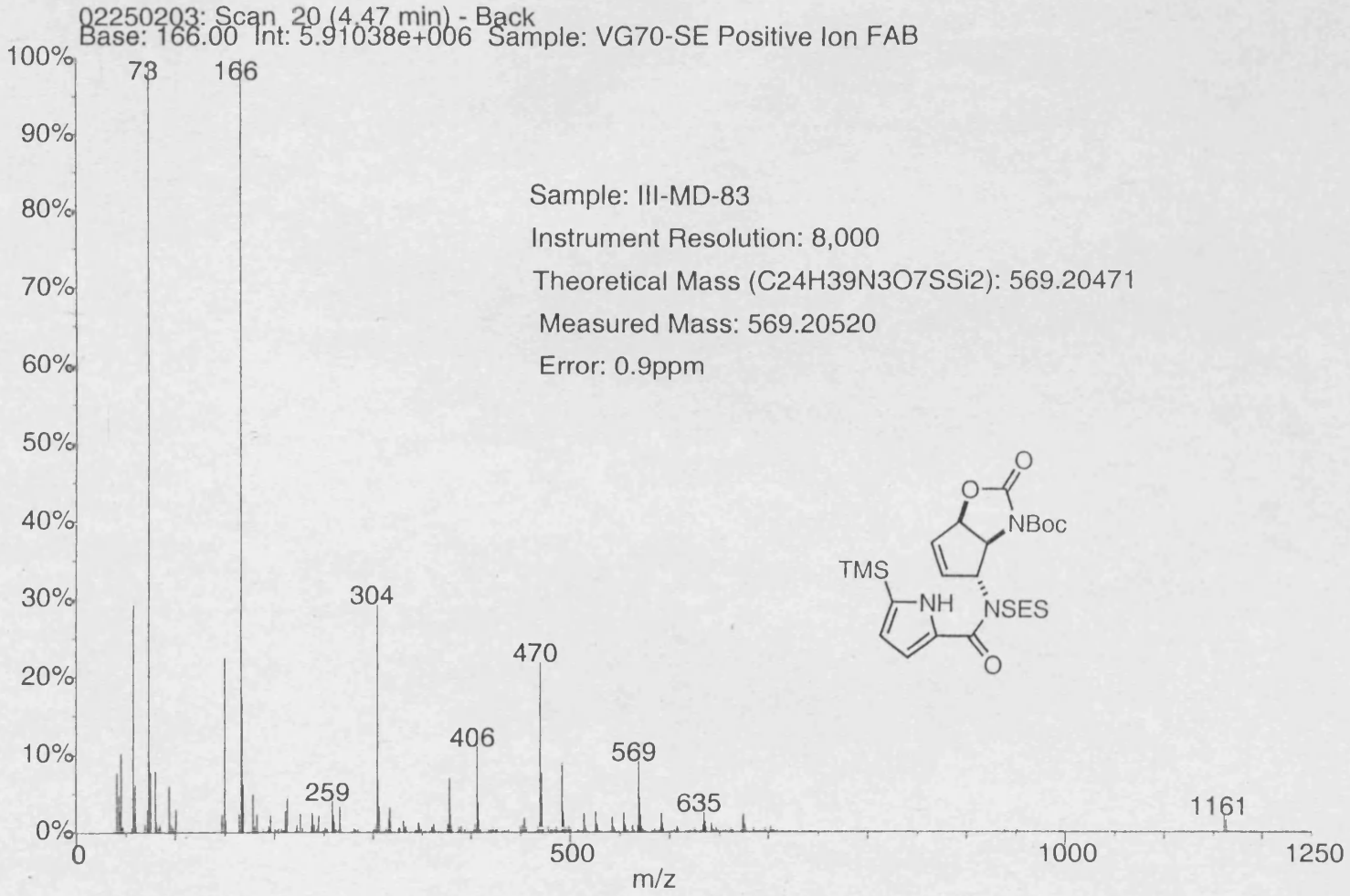




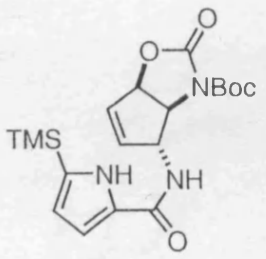
PERKIN ELMER



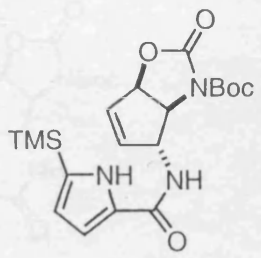
03/02/24 15: 12
X: 16 scans, 16.0cm-1, apod none


02250203: Scan 20 (4.47 min) - Back
Base: 166.00 Int: 5.91038e+006 Sample: VG70-SE Positive Ion FAB
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
73
166
304
470
406
569
259
635
1161
0
500
1000
1250
m/z
Sample: III-MD-83
Instrument Resolution: 8,000
Theoretical Mass (C24H39N3O7SSi2): 569.20471
Measured Mass: 569.20520
Error: 0.9ppm
O
O
NBoc
TMS
NH
NSES
O

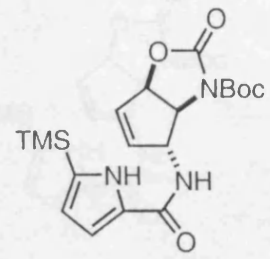
III-md-84
CDCl3, 298 K

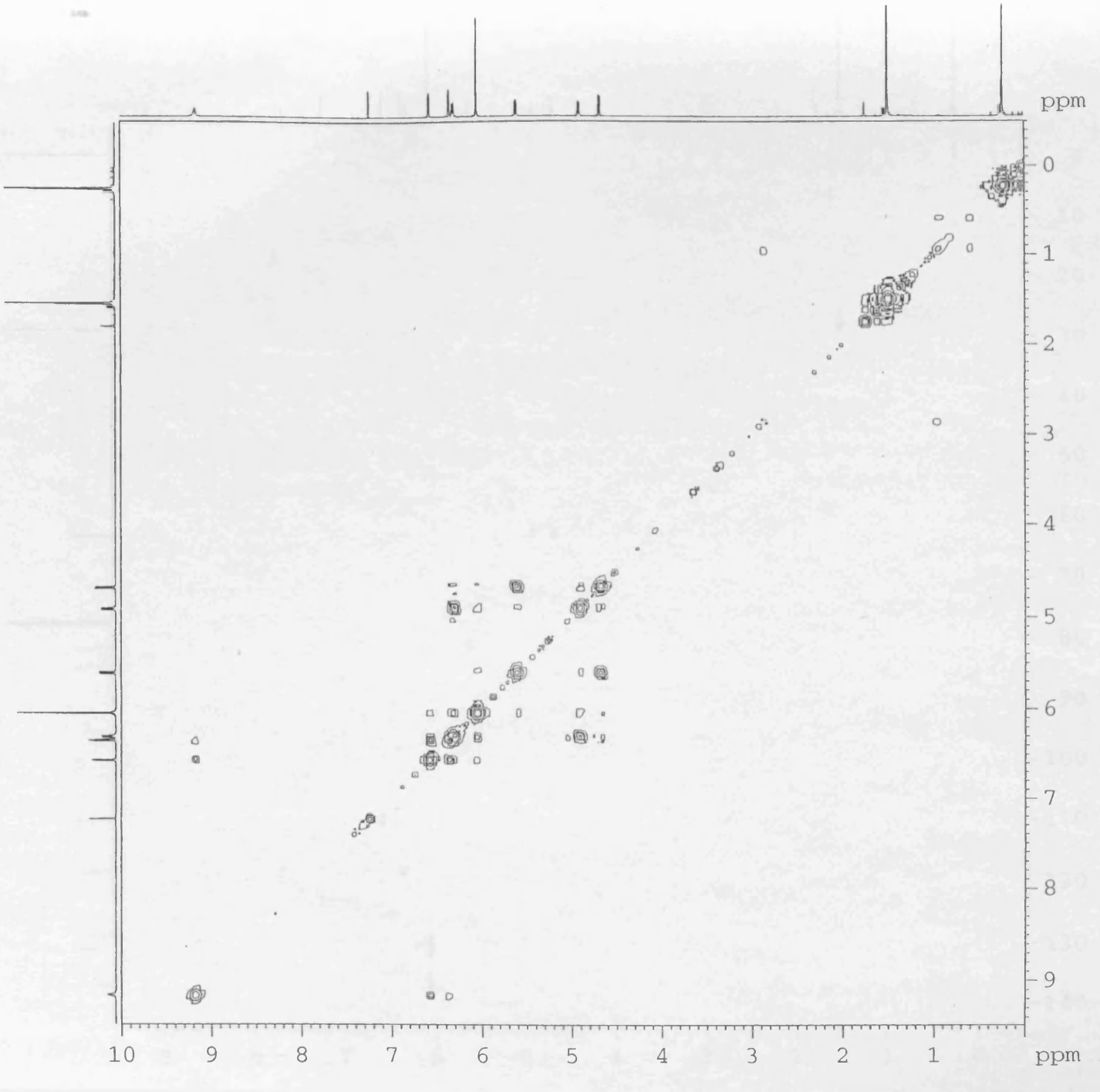


III-md-84
CDCl3, 298 K

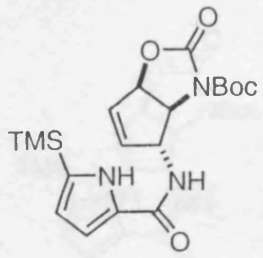


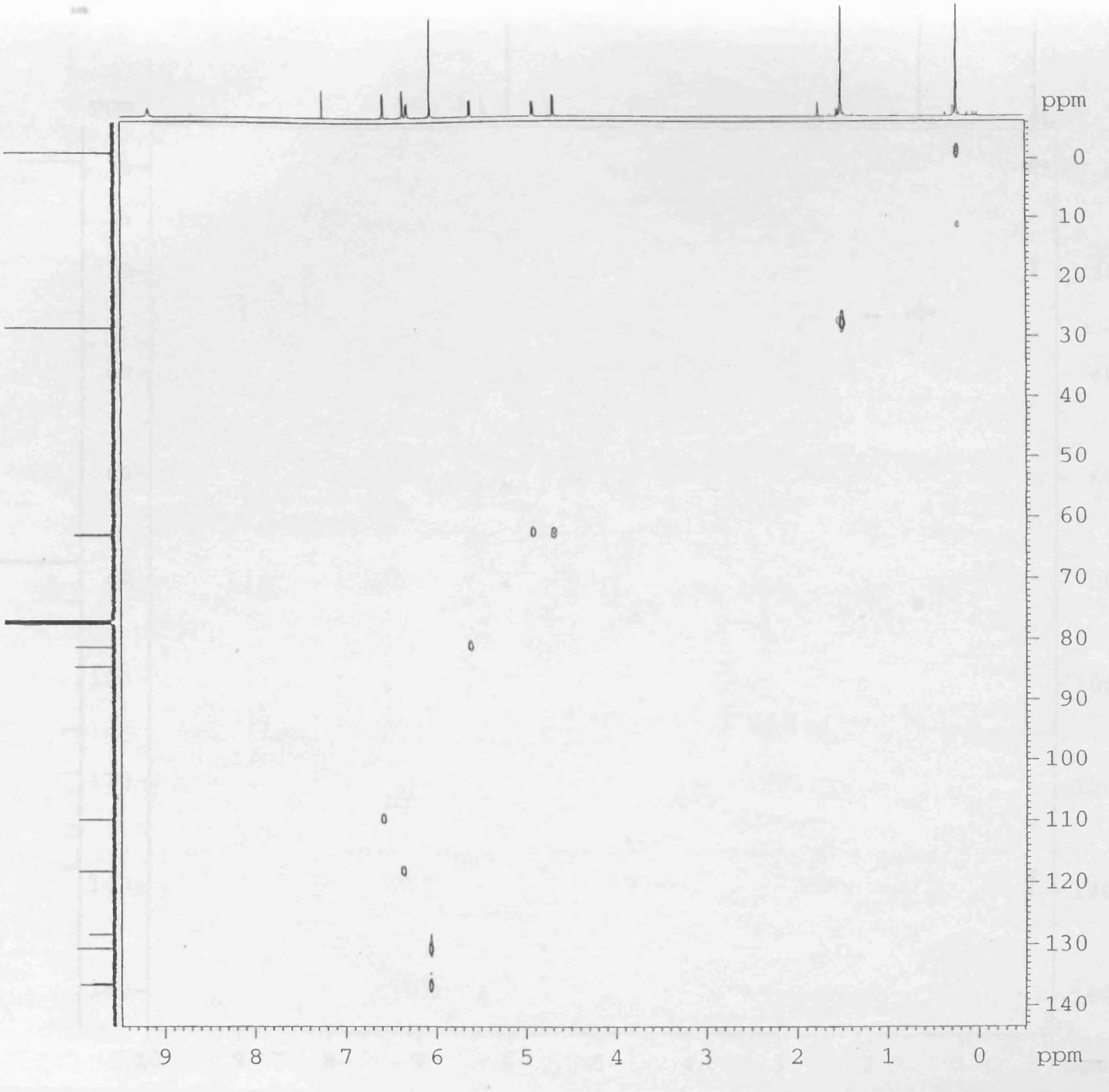
III-md-84
CDCl3, 298 K
COSY



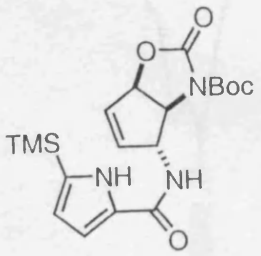


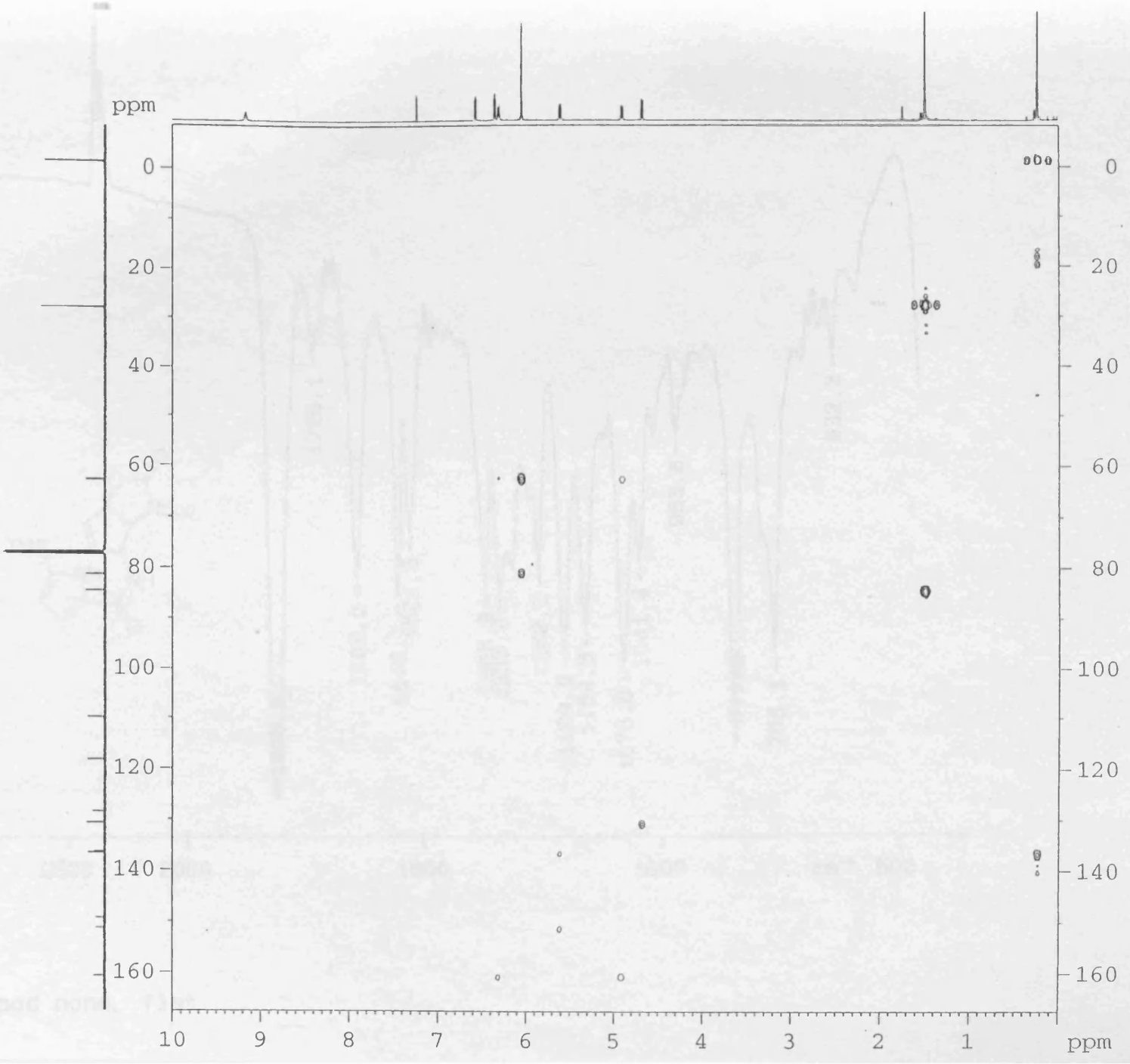
III-md-84
CDCl3, 298 K
HMQC



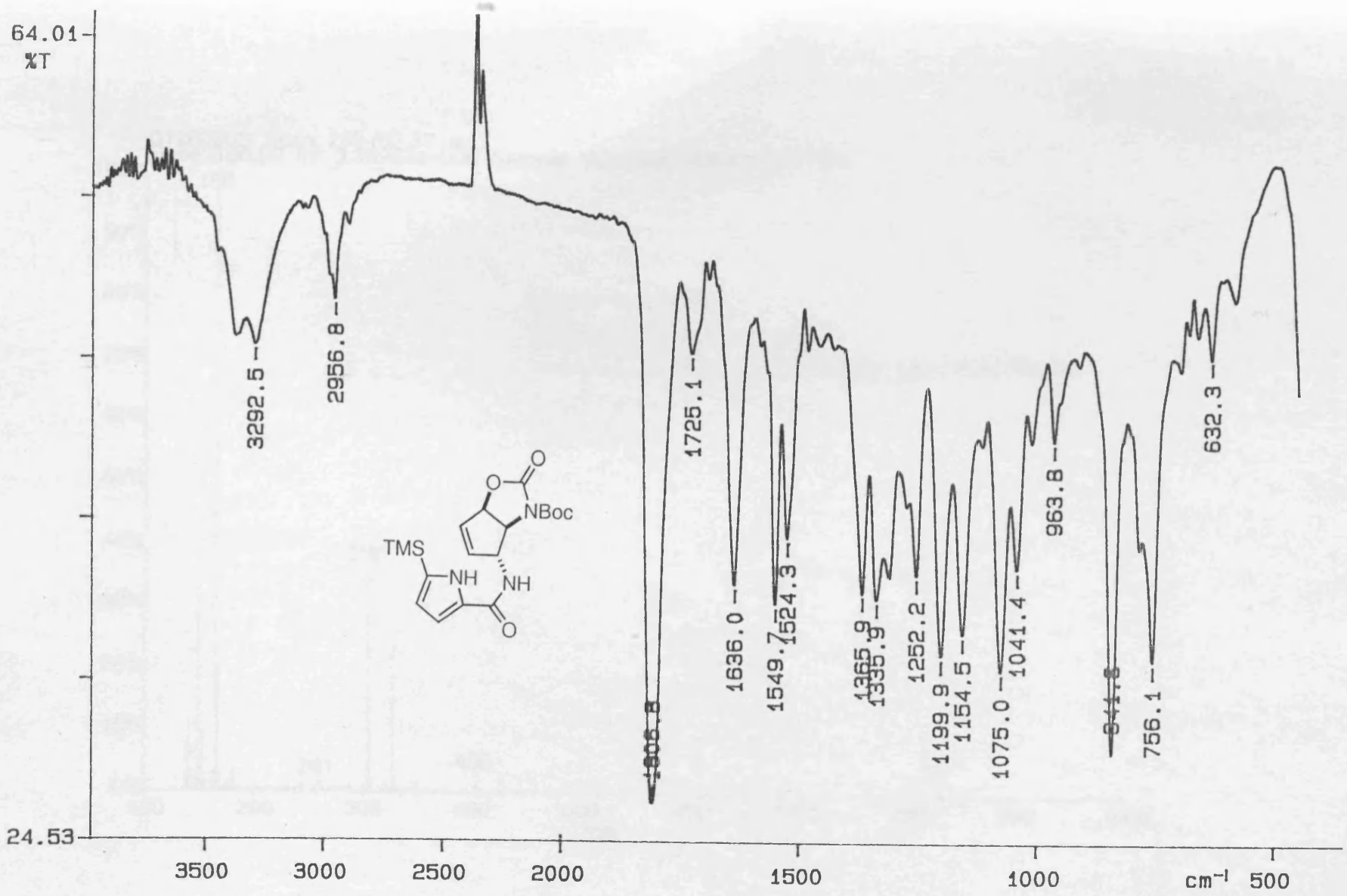


III-md-84
CDCl3, 298 K
HMBC

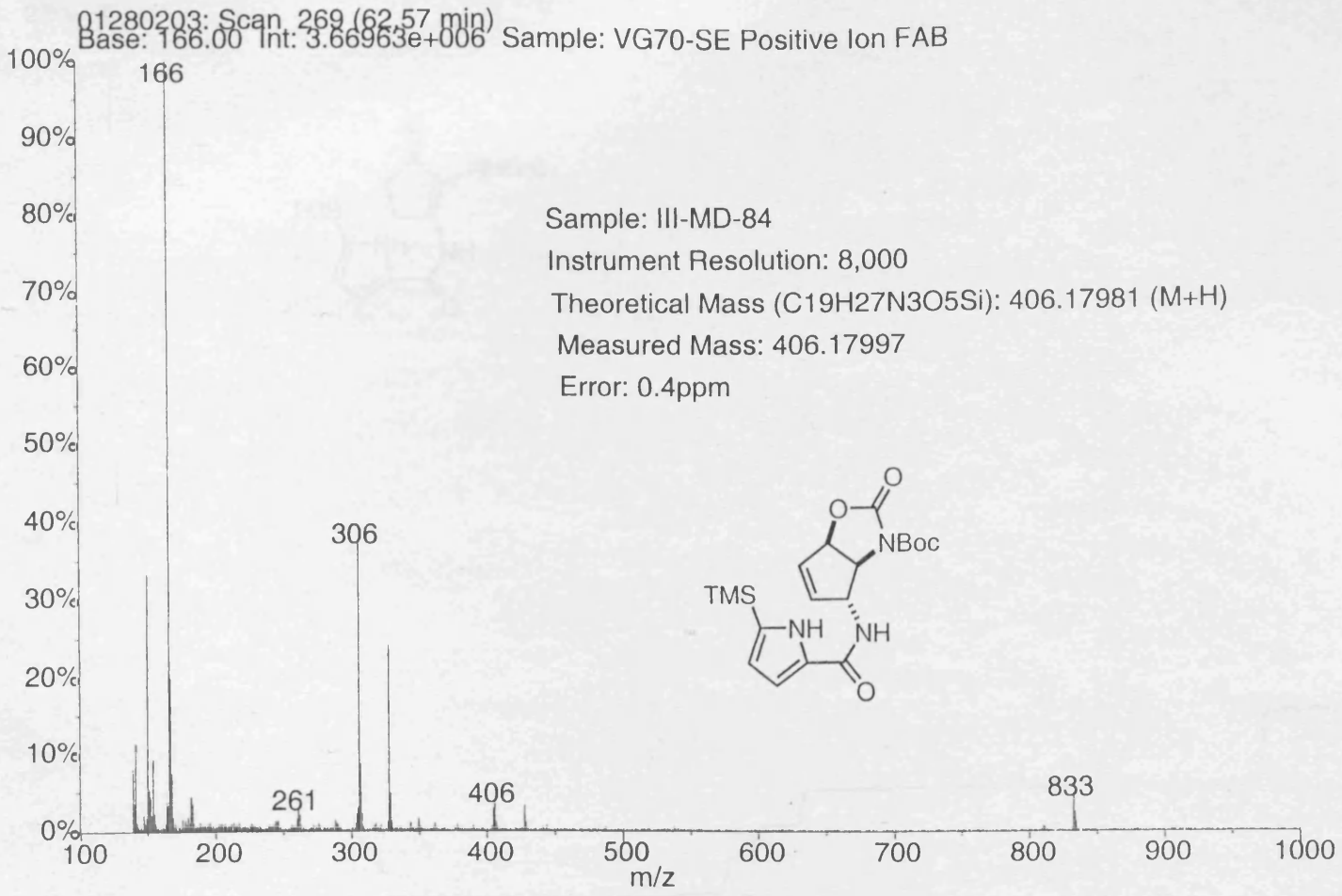




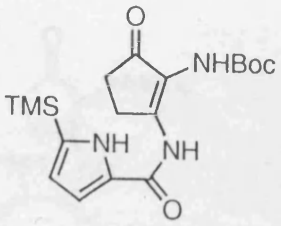
PERKIN ELMER



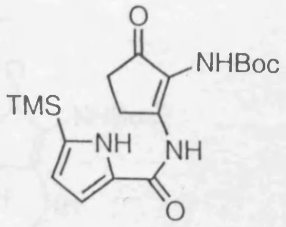
03/02/26 13: 12
X: 16 scans, 16.0cm-1, apod none, flat


01280203: Scan 269 (62.57 min)
Base: 166.00 Int: 3.66963e+006
Sample: VG70-SE Positive Ion FAB
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
166
306
261
406
833
100
200
300
400
500
600
700
800
900
1000
m/z
Sample: III-MD-84
Instrument Resolution: 8,000
Theoretical Mass (C19H27N3O5Si): 406.17981 (M+H)
Measured Mass: 406.17997
Error: 0.4ppm
O
O
NBoc
TMS
NH
NH
O

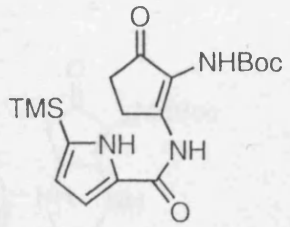
III-md-96a
CDCl3, 298 K

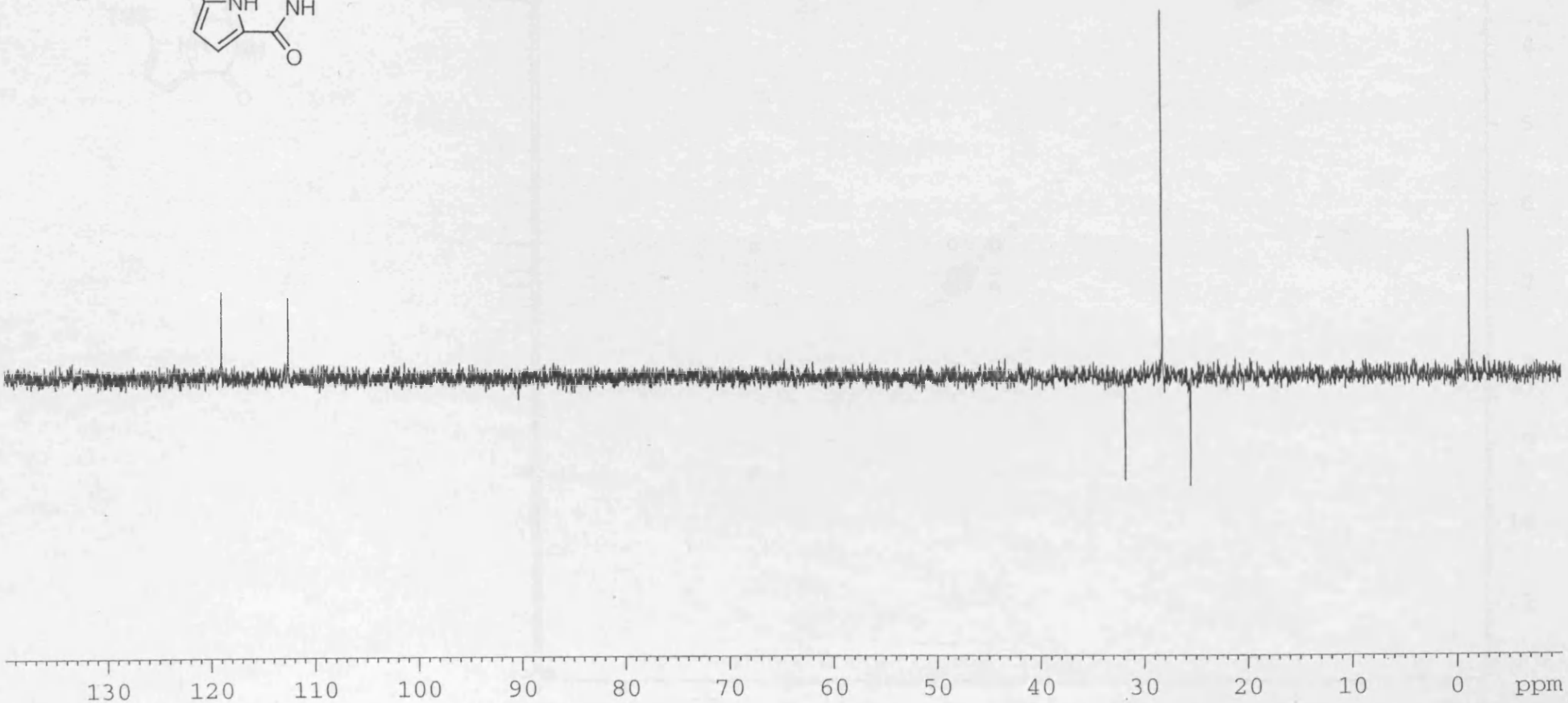


III-md-96a
CDCl3, 298 K

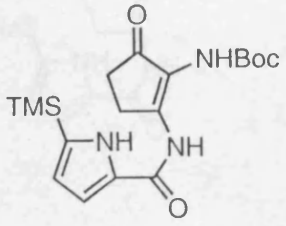


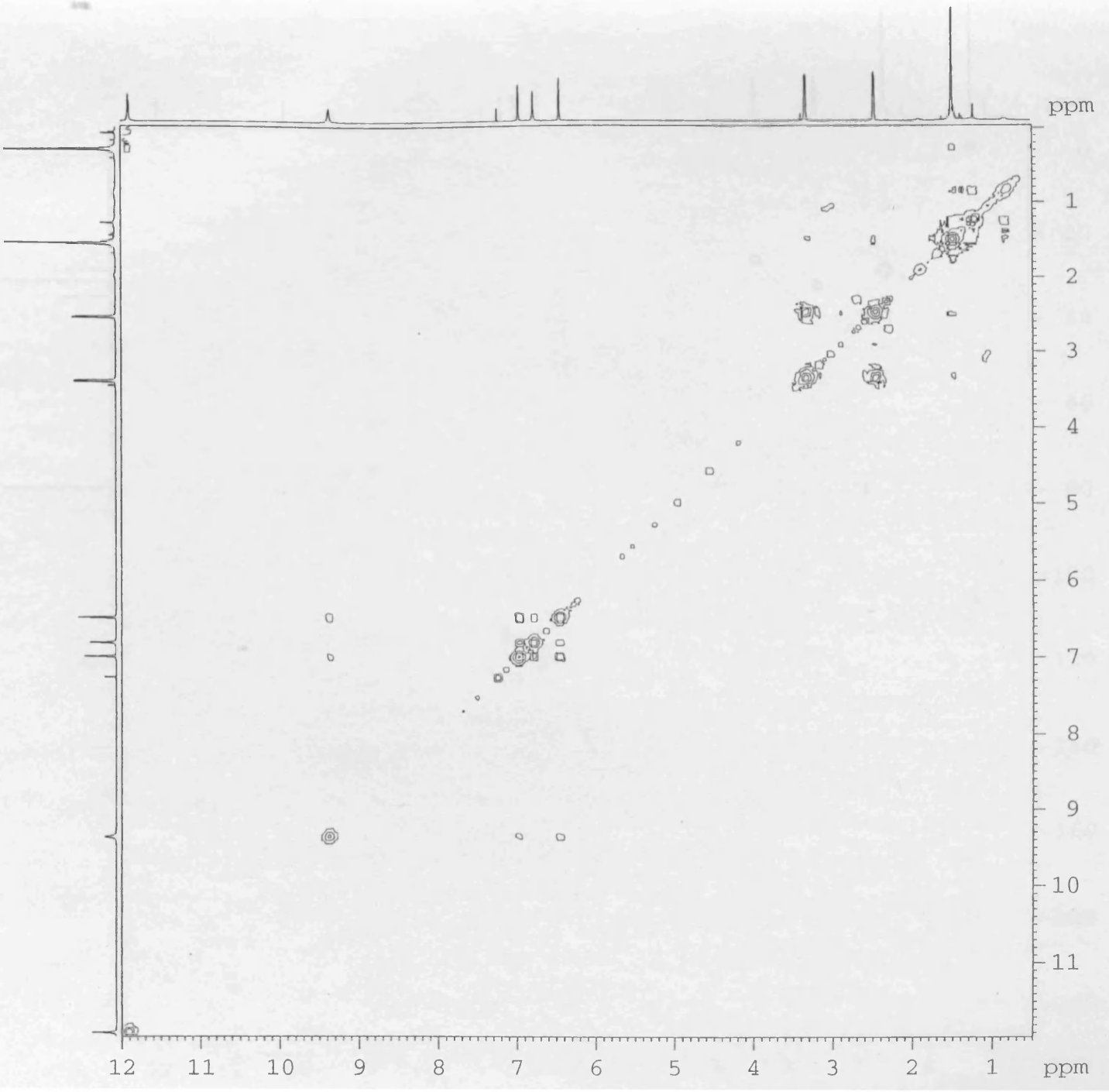
III-md-96a
CDCl3, 298 K



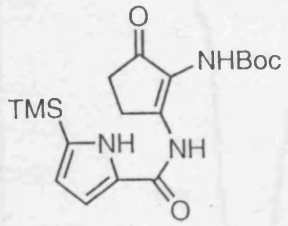


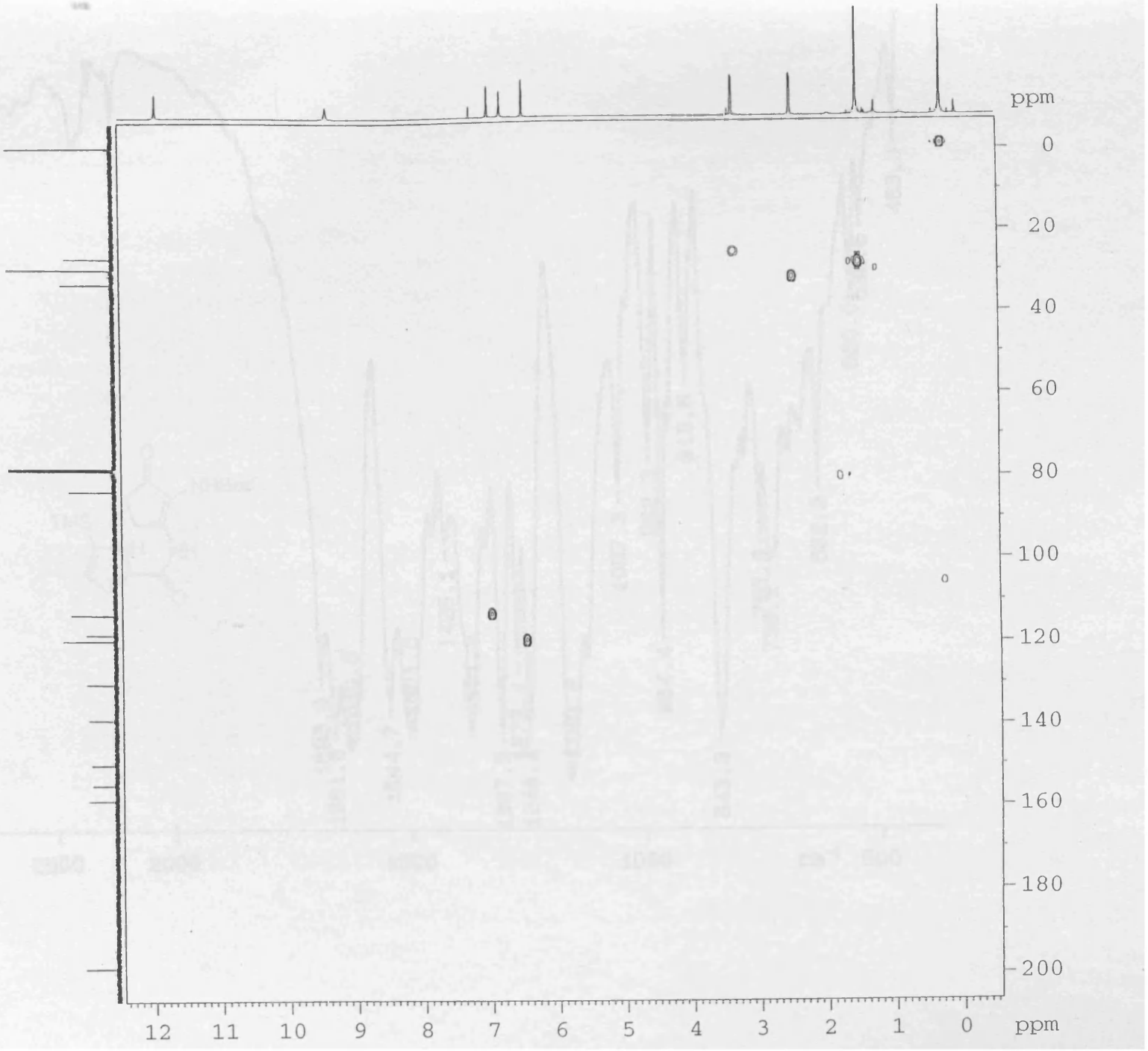
III-md-96a
CDCl3, 298 K
COSY

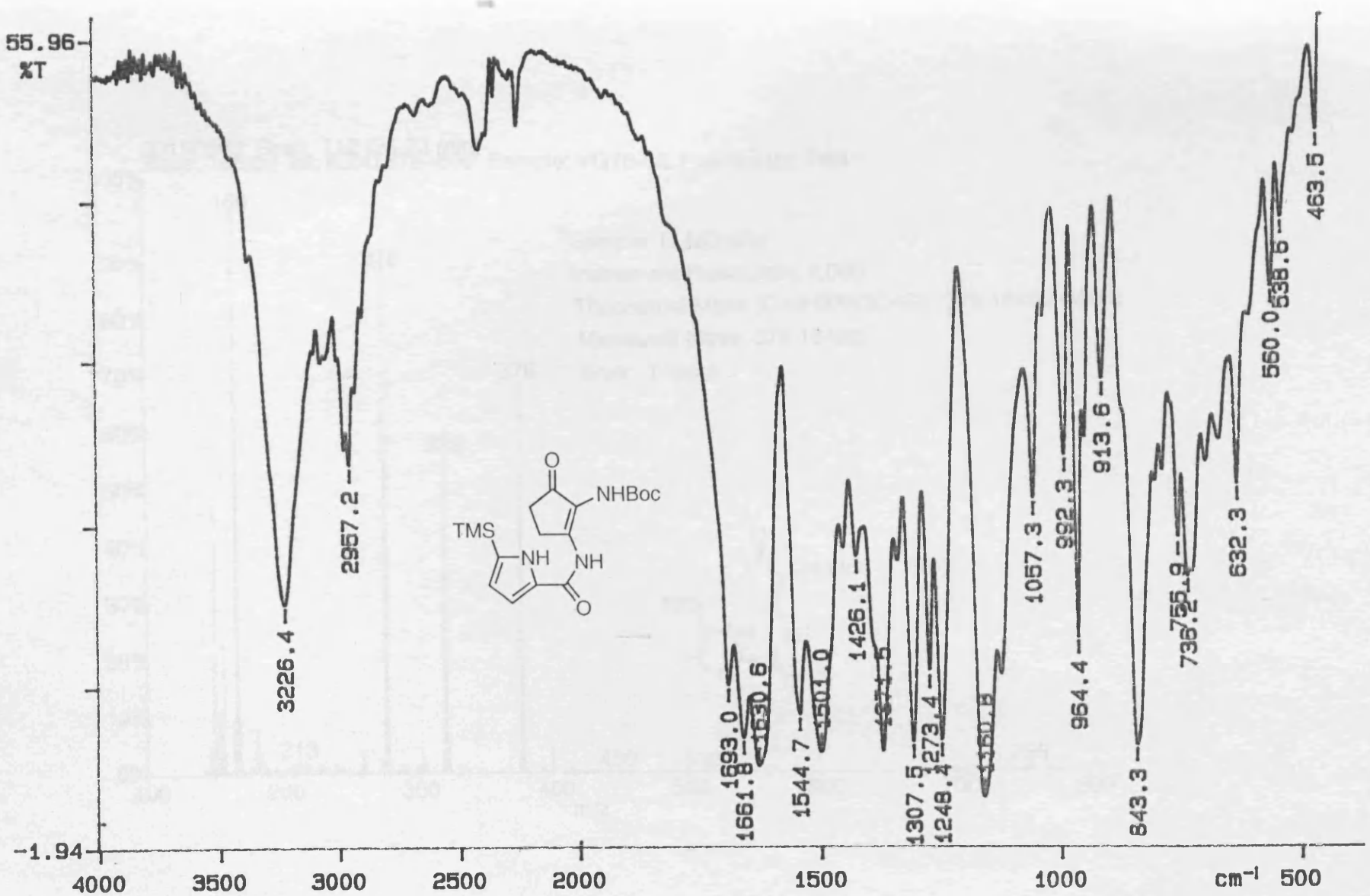


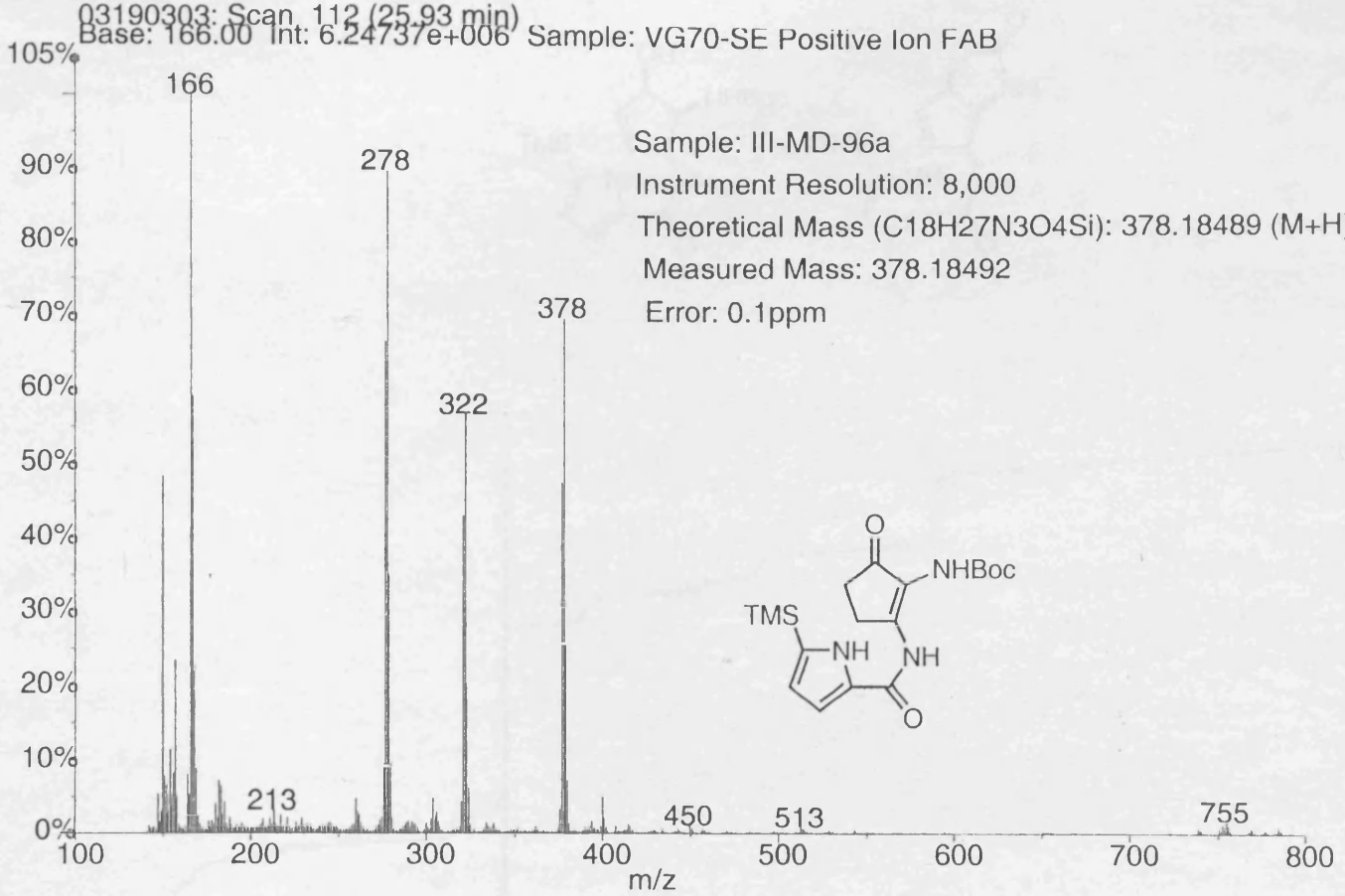


III-md-96a
CDCl3, 298 K
HMQC

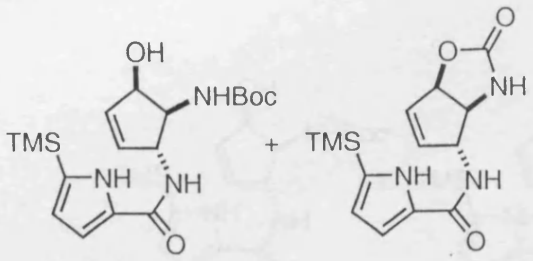




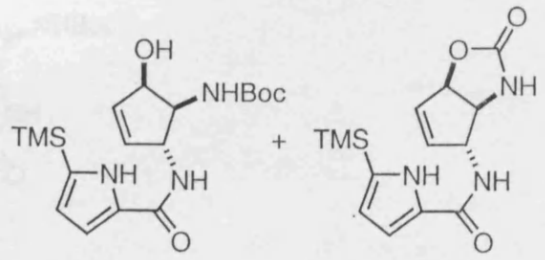

55.96
%T
-1.94
4000
3500
3000
2500
2000
1500
1000
500
cm-1
3226.4
2957.2
1693.0
1661.8
1630.6
1544.7
1501.0
1426.1
1307.5
1273.4
1248.4
1057.3
992.3
964.4
913.6
843.3
755.9
738.2
632.3
560.0
538.5
463.5
NHBoc
TMS
NH
NH
O
O


03190303: Scan 112 (25.93 min)
Base: 166.00 Int: 6.24737e+006 Sample: VG70-SE Positive Ion FAB
105%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
166
278
378
322
213
450
513
755
100
200
300
400
500
600
700
800
m/z
Sample: III-MD-96a
Instrument Resolution: 8,000
Theoretical Mass (C18H27N3O4Si): 378.18489 (M+H)
Measured Mass: 378.18492
Error: 0.1ppm
O
NHBoc
TMS
NH
NH
O

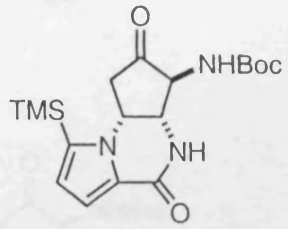
III-md-86 (mixture)
MeOD, 298 K



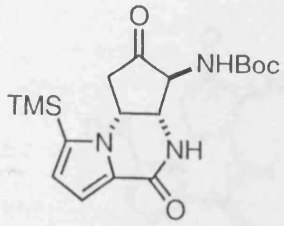
III-md-86 (mixture)
MeOD, 298 K



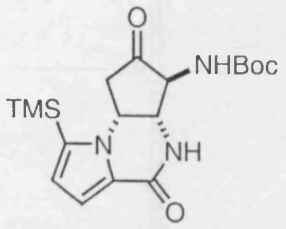
III-md-96b
MeOD, 298 K



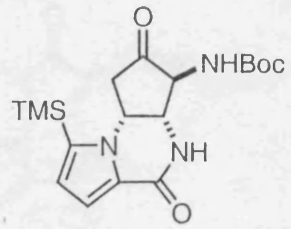
III-md-96b
MeOD, 298 K

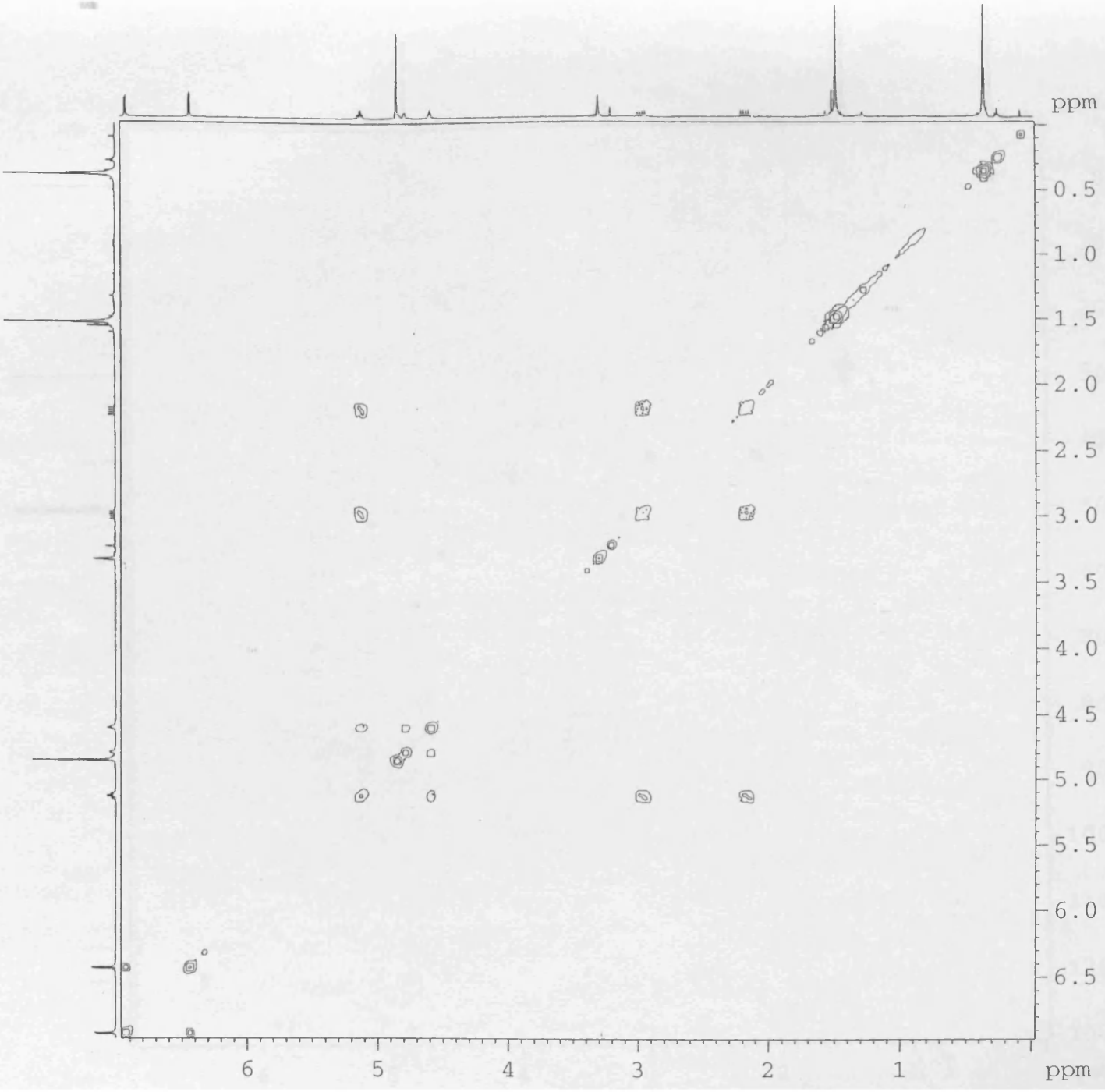


III-md-96b
MeOD, 298 K
DEPT

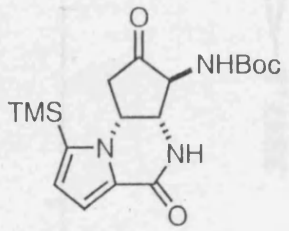


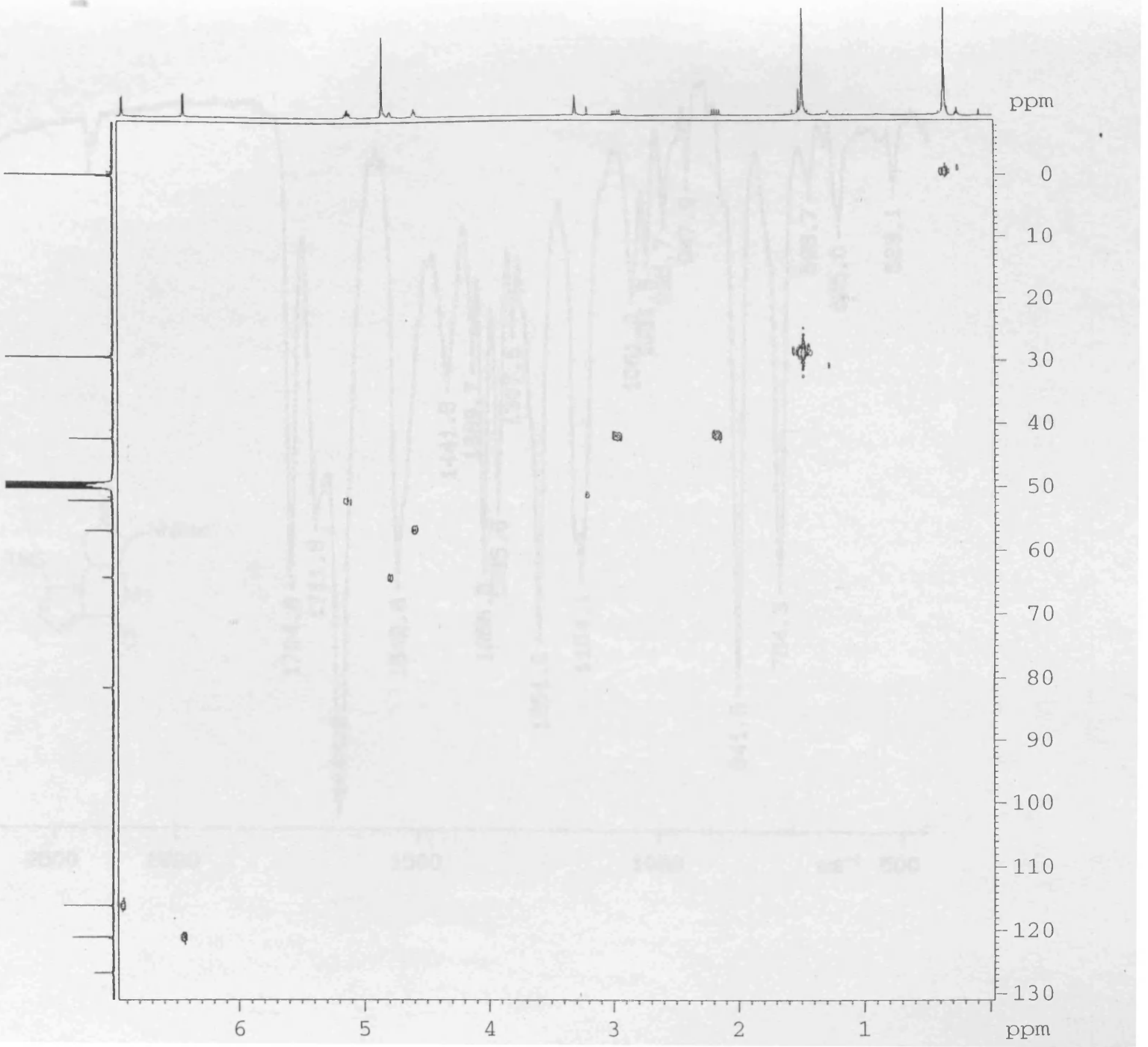
III-md-96b
MeOD, 298 K
COSY

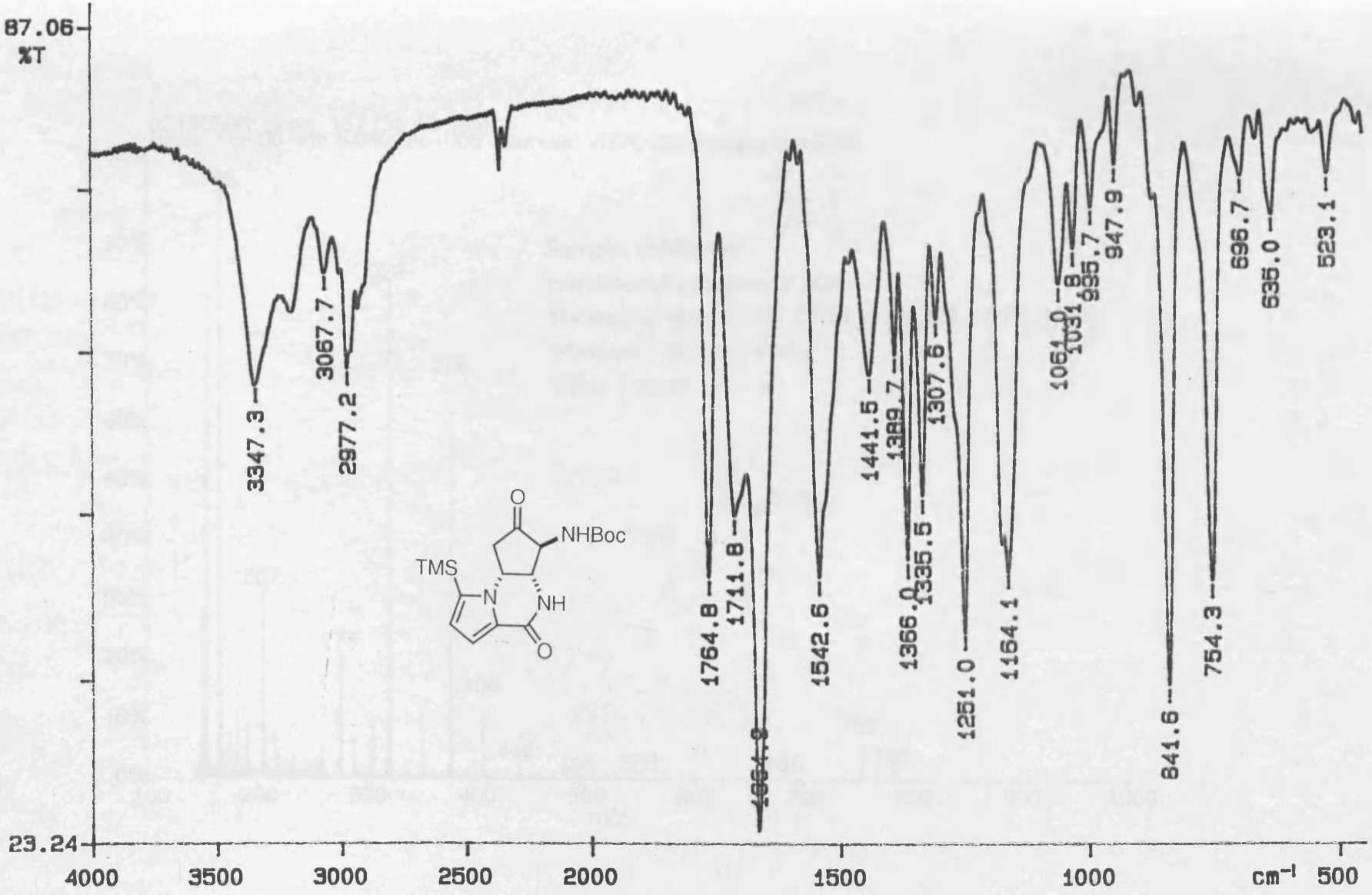


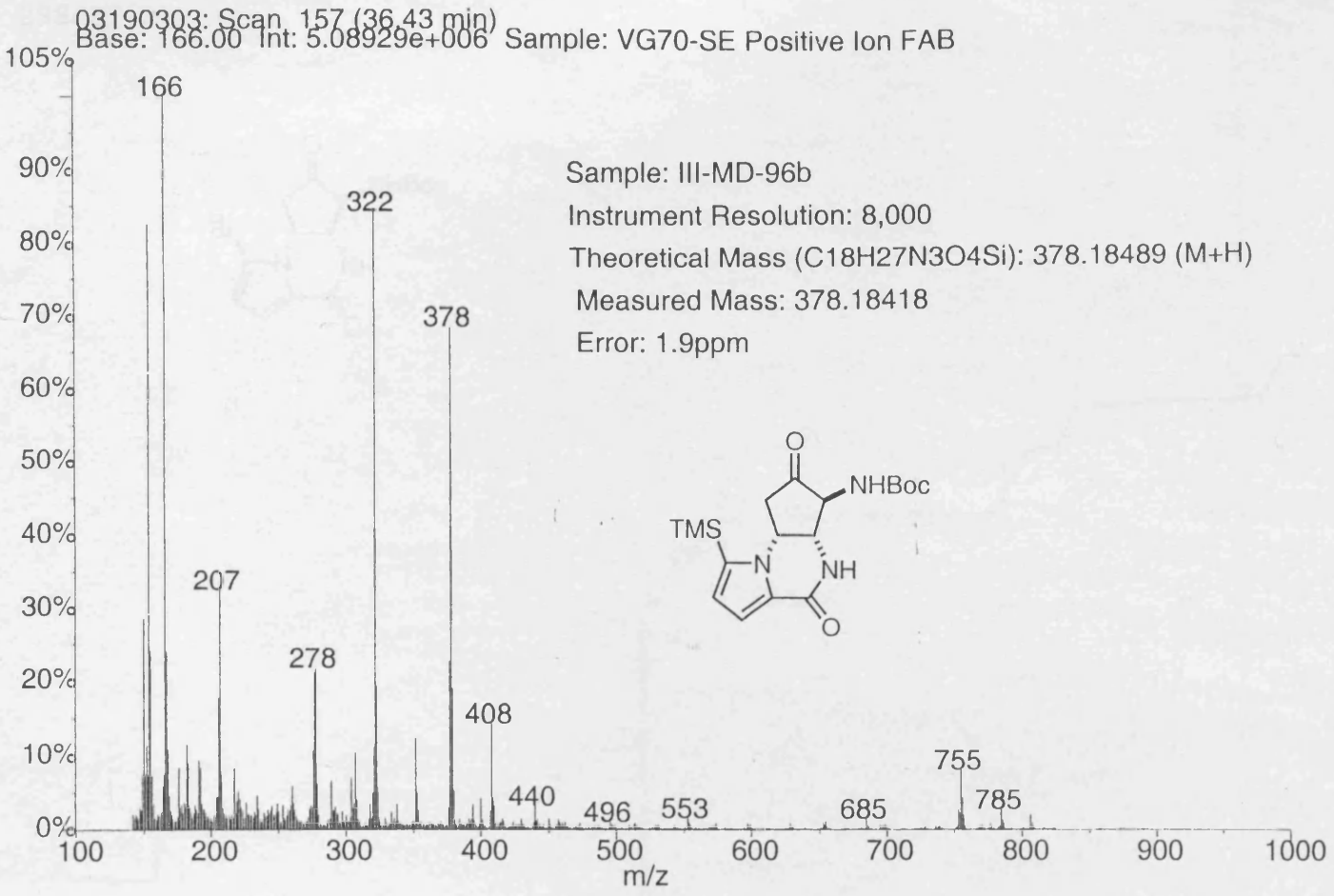


III-md-96b
MeOD, 298 K
HMQC

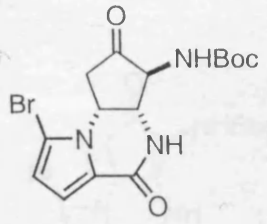




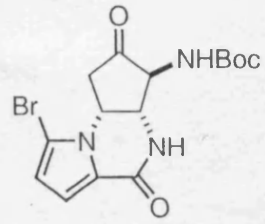

87.06
%T
23.24
3347.3
3067.7
2977.2
1764.8
1711.8
1542.6
1441.5
1389.7
1366.0
1335.5
1307.6
1251.0
1164.1
1061.0
1031.8
995.7
947.9
841.6
754.3
696.7
635.0
523.1
4000
3500
3000
2500
2000
1500
1000
cm-1
500
TMS
NHBoc
NH
O
O
N


03190303: Scan 157 (36.43 min)
Base: 166.00 Int: 5.08929e+006 Sample: VG70-SE Positive Ion FAB
105%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
166
322
378
207
278
408
440
496
553
685
755
785
100
200
300
400
500
600
700
800
900
1000
m/z
Sample: III-MD-96b
Instrument Resolution: 8,000
Theoretical Mass (C18H27N3O4Si): 378.18489 (M+H)
Measured Mass: 378.18418
Error: 1.9ppm
O
NHBoc
TMS
N
NH
O

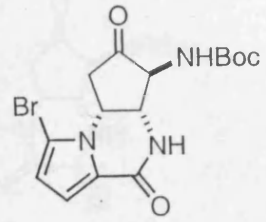
III-md-97
MeOD, 298 K

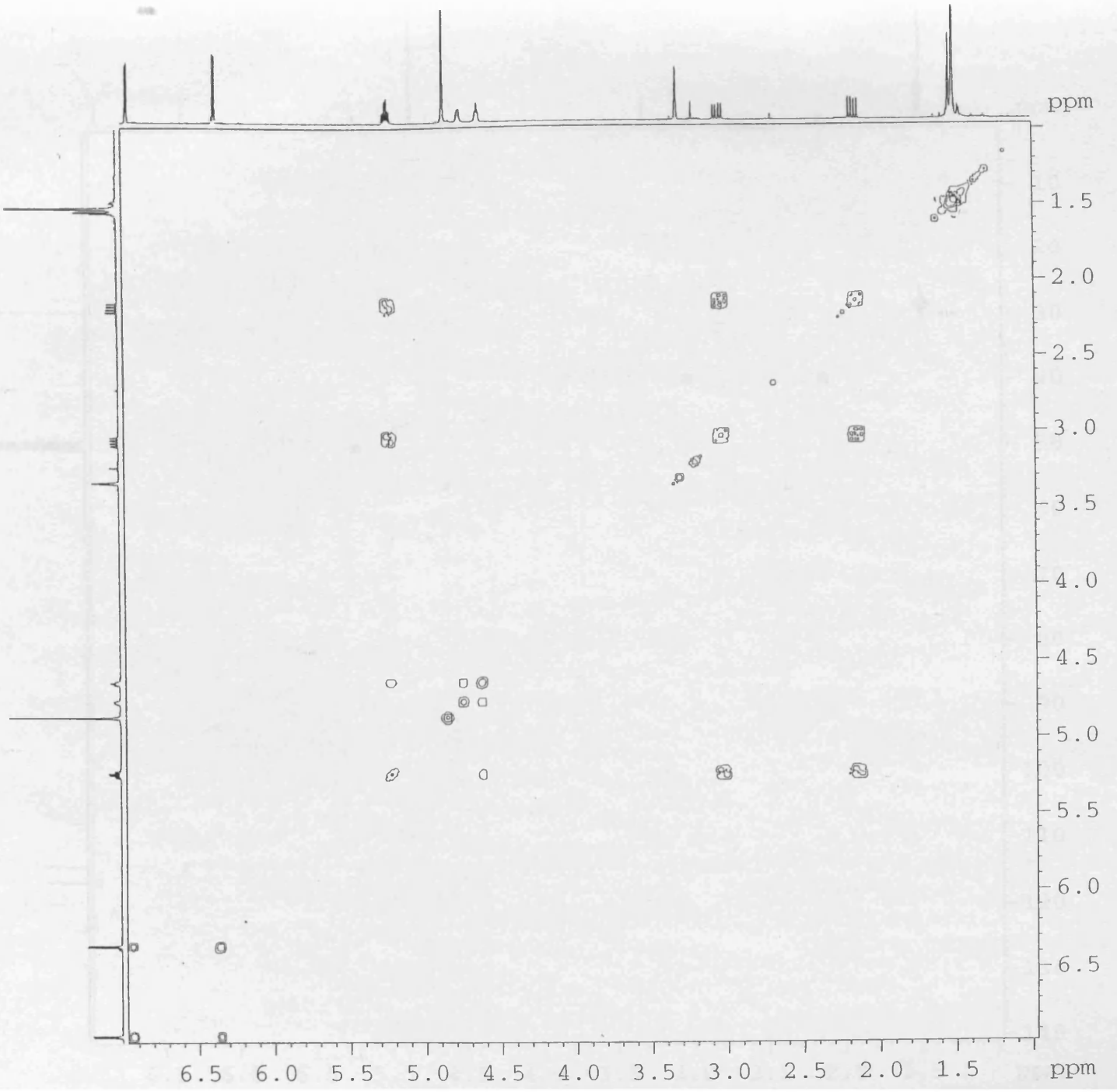


III-md-97
MeOD, 298 K

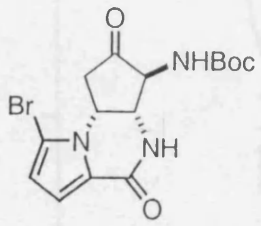


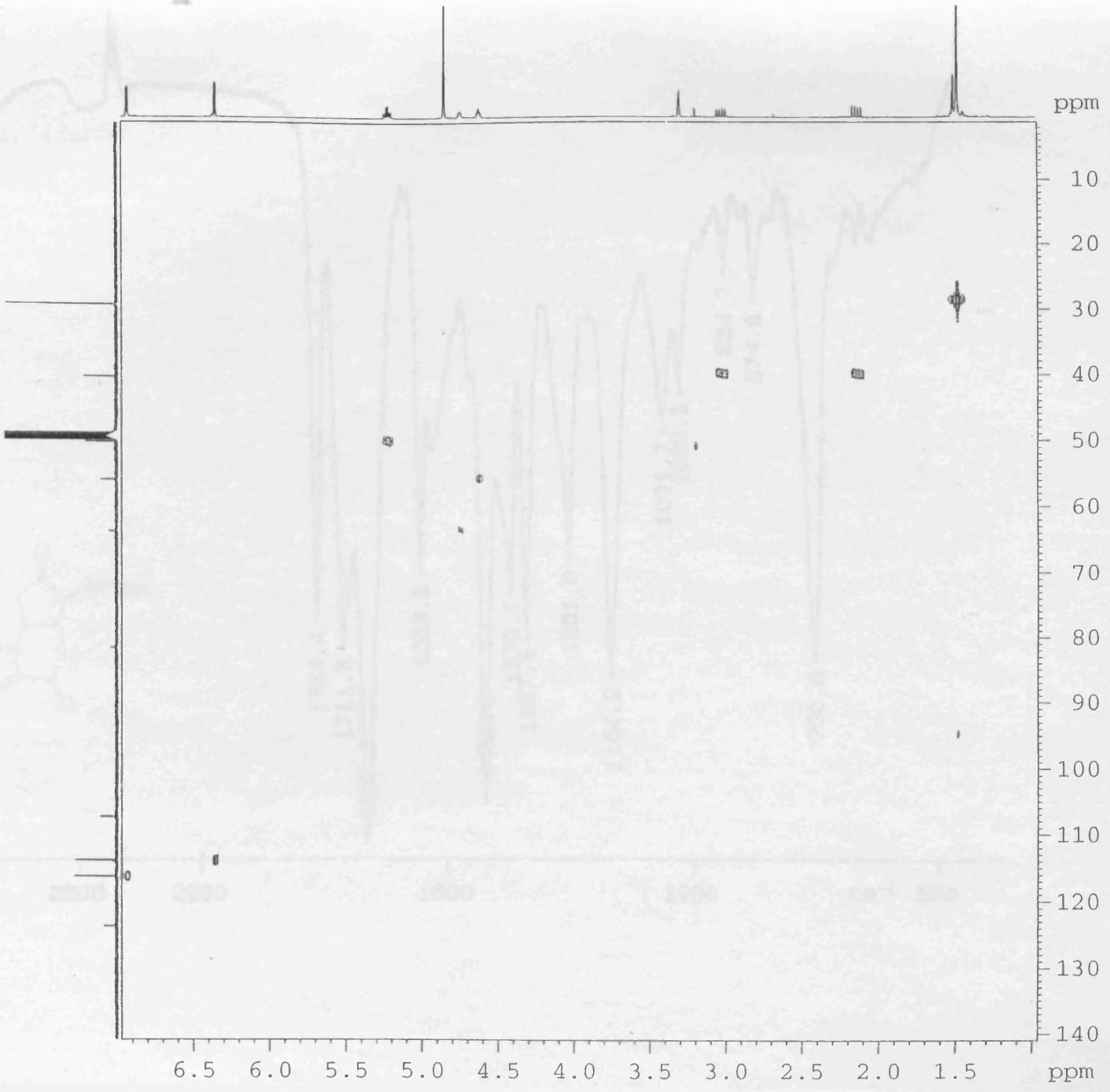
III-md-97
MeOD, 298 K
COSY

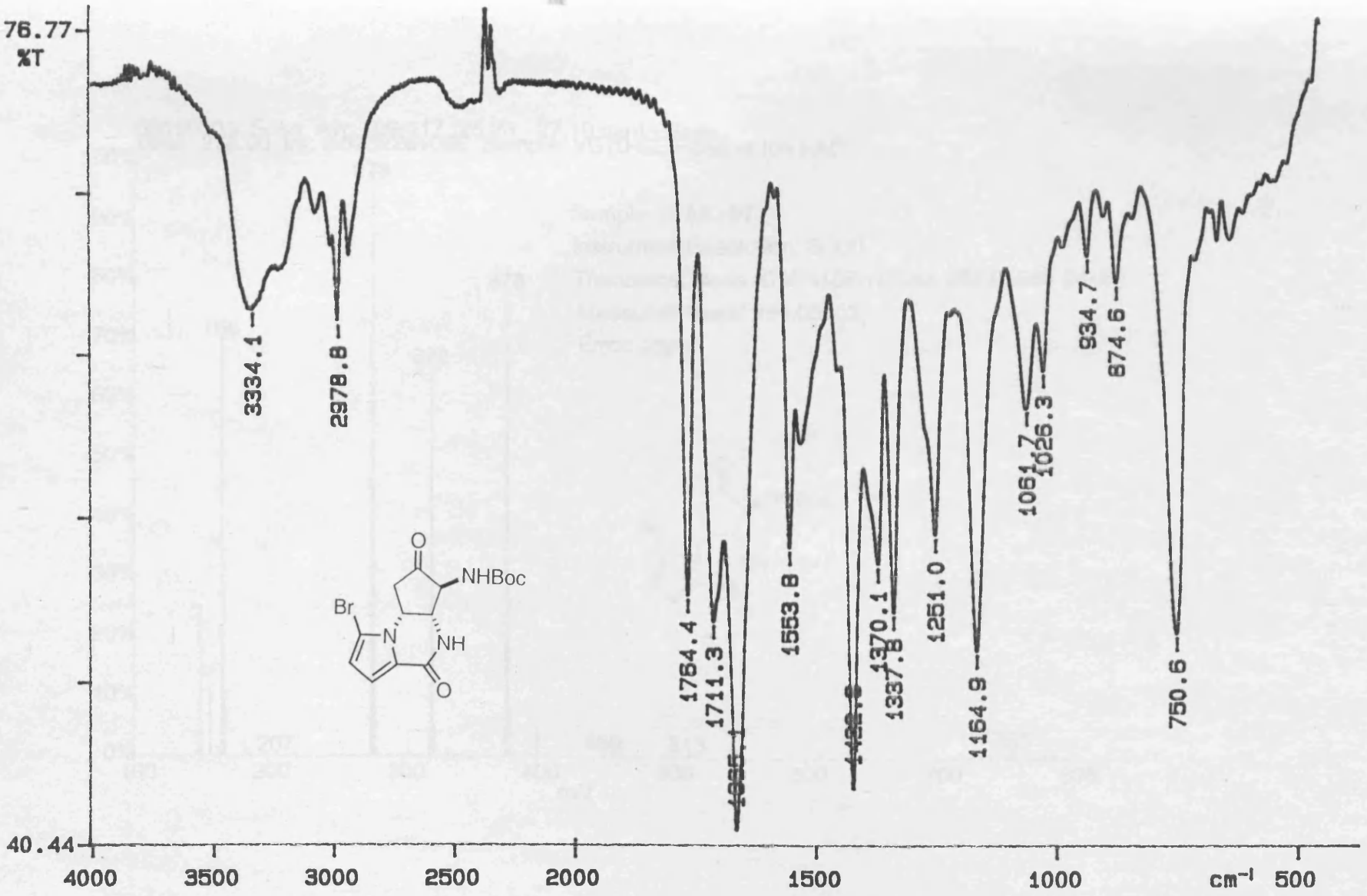


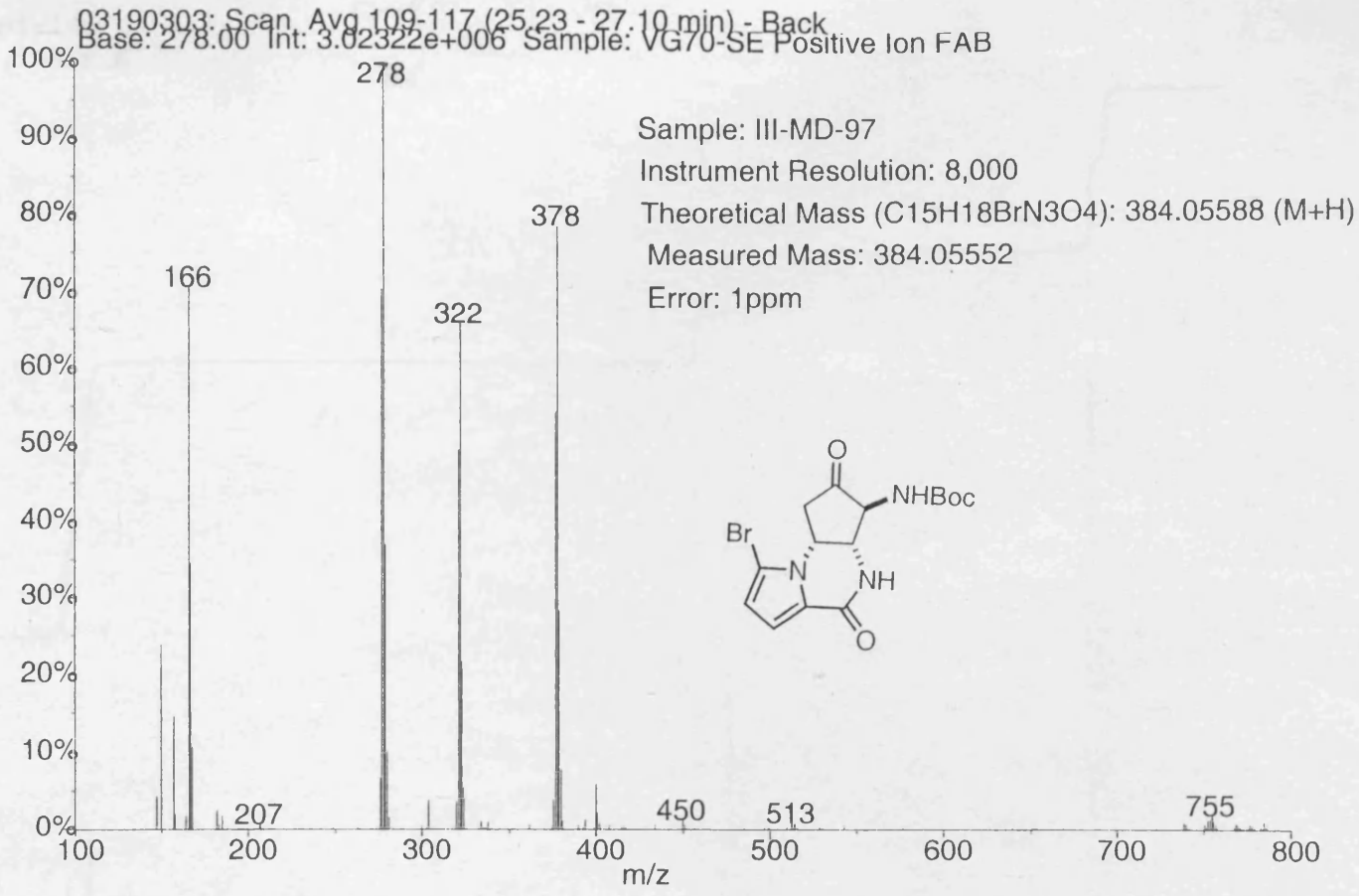


III-md-97
MeOD, 298 K
HMQC

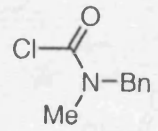


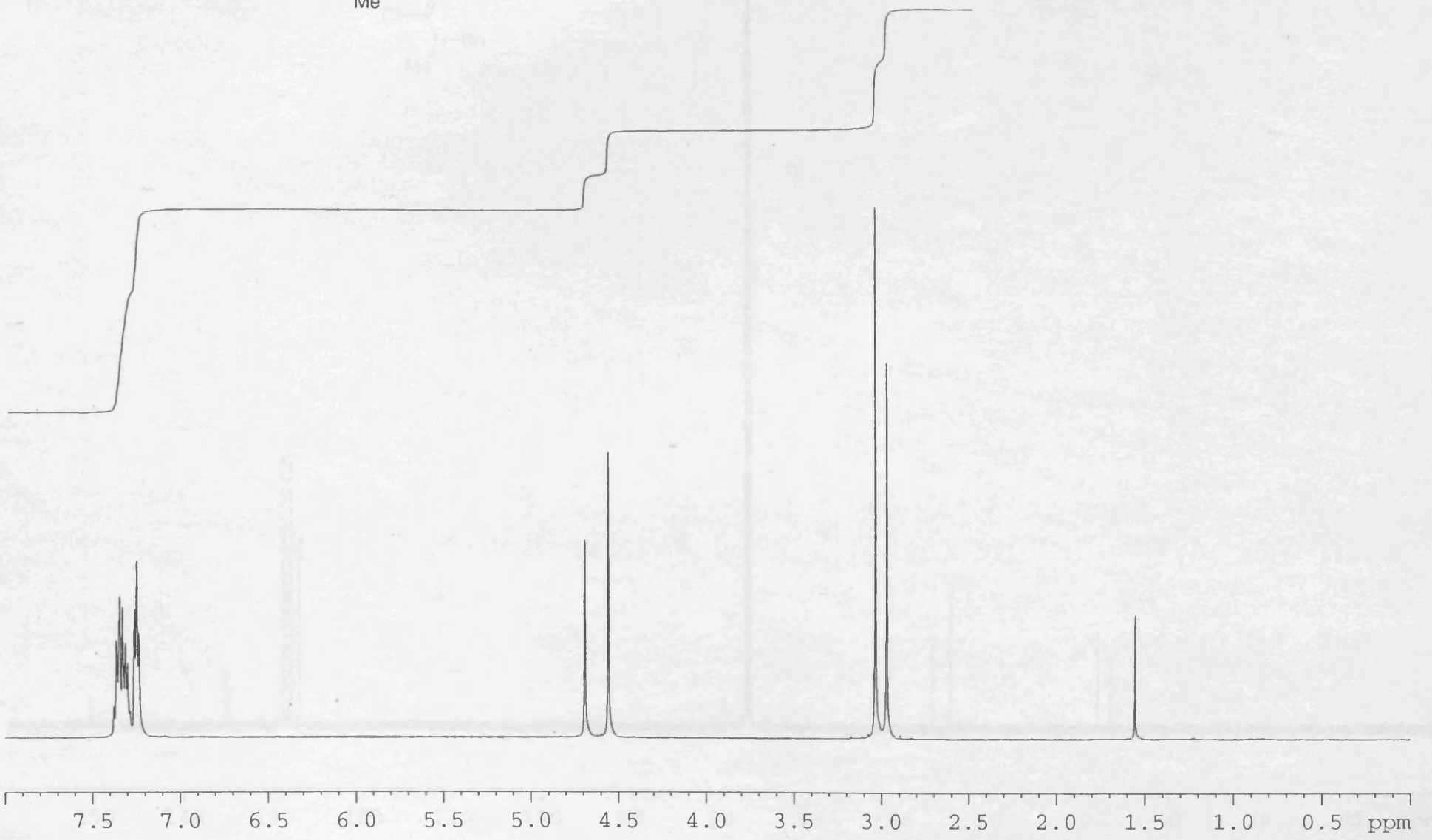



76.77
%T
40.44
3334.1
2978.8
1784.4
1711.3
1553.8
1370.1
1337.8
1251.0
1164.9
1061.7
1026.3
934.7
874.6
750.6
4000
3500
3000
2500
2000
1500
1000
cm-1
500
Br
N
NH
NHBoc
O
O

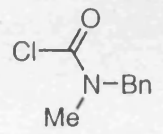

03190303: Scan, Avg 109-117 (25.23 - 27.10 min) - Back
Base: 278.00 Int: 3.02322e+006 Sample: VG70-SE Positive Ion FAB
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
278
378
166
322
207
450
513
755
100
200
300
400
500
600
700
800
m/z
Sample: III-MD-97
Instrument Resolution: 8,000
Theoretical Mass (C15H18BrN3O4): 384.05588 (M+H)
Measured Mass: 384.05552
Error: 1ppm
O
NHBoc
Br
N
NH
O

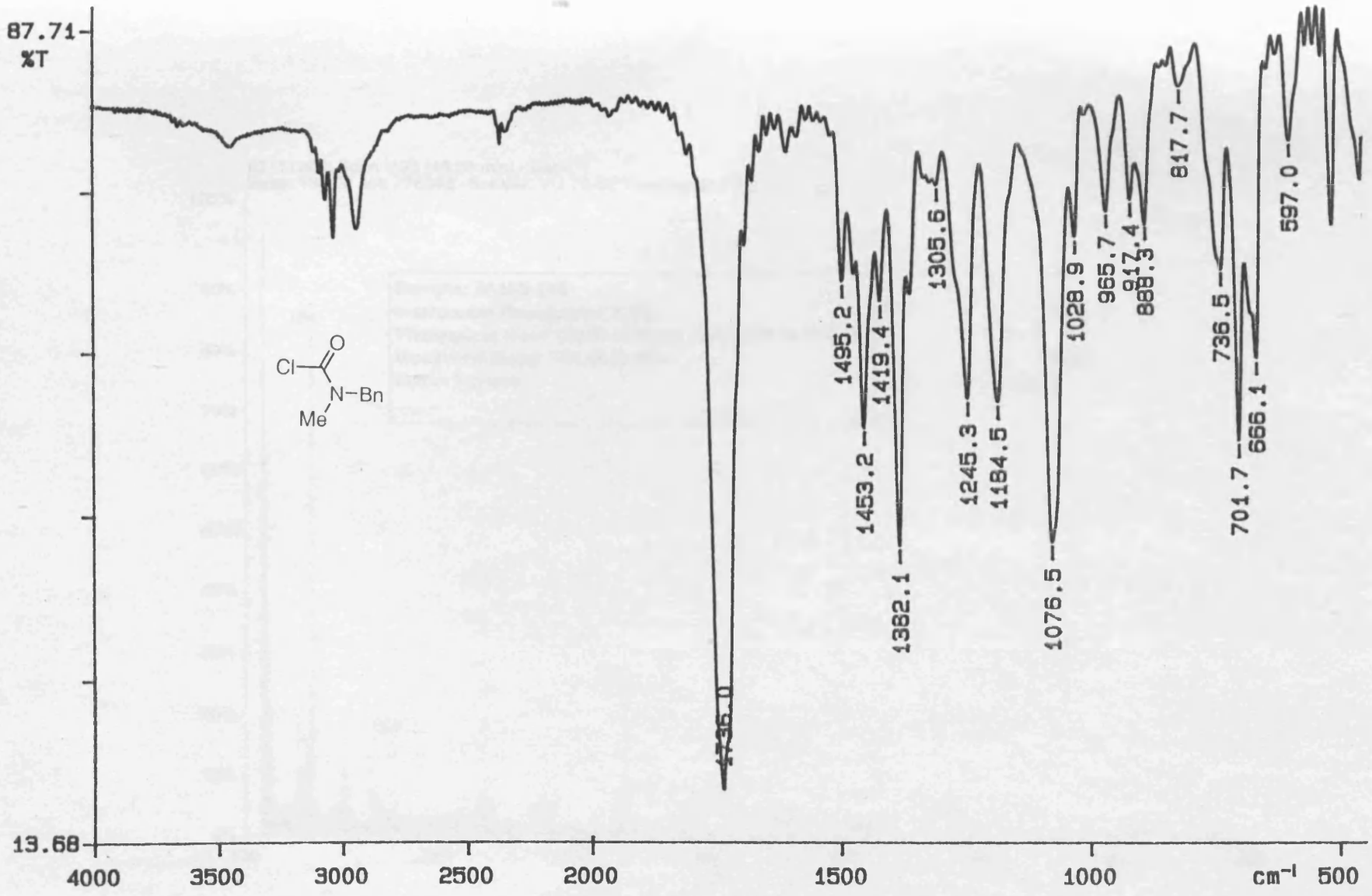
IV-md-148
CDCl3, 298 K

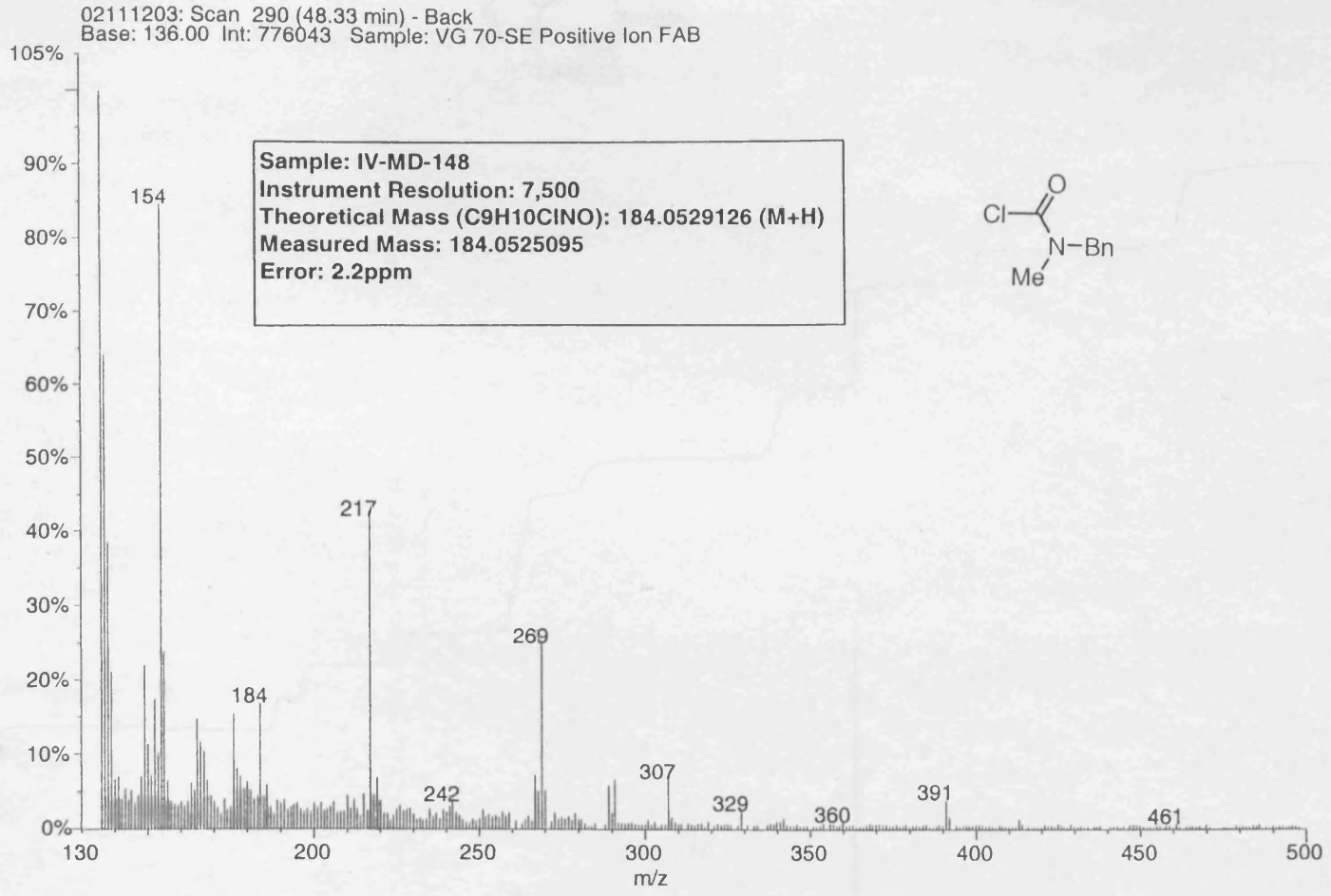




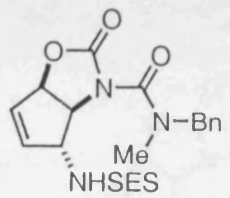
IV-md-148
CDCl3, 298 K

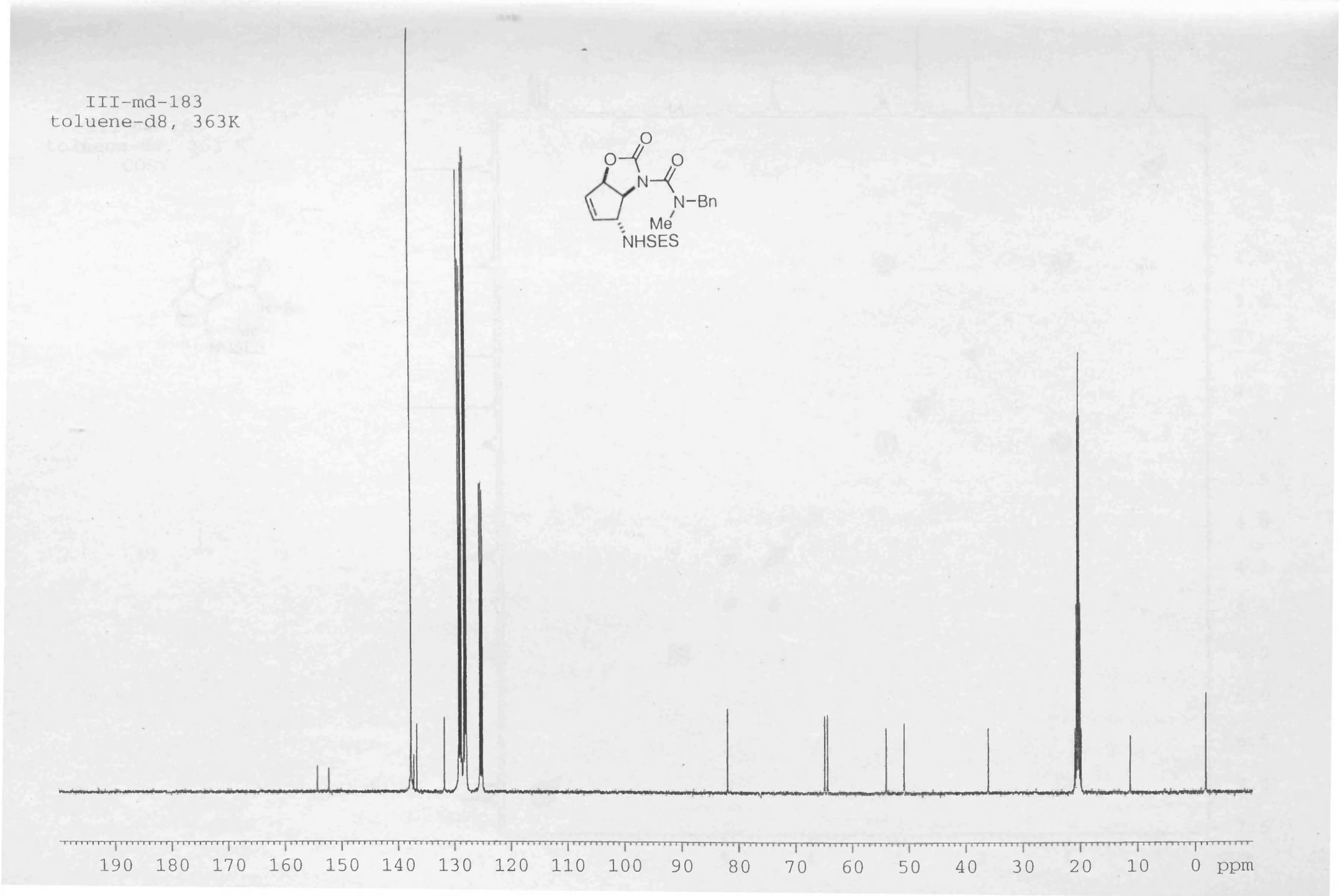



87.71
%T
13.68
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
500
Cl
O
N–Bn
Me
1736.0
1495.2
1453.2
1419.4
1382.1
1305.6
1245.3
1184.5
1076.5
1028.9
965.7
917.4
888.3
817.7
736.5
701.7
666.1
597.0

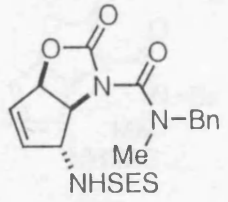

02111203: Scan 290 (48.33 min) - Back
Base: 136.00 Int: 776043 Sample: VG 70-SE Positive Ion FAB
Sample: IV-MD-148
Instrument Resolution: 7,500
Theoretical Mass (C9H10ClNO): 184.0529126 (M+H)
Measured Mass: 184.0525095
Error: 2.2ppm
Cl
O
N−Bn
Me
105%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
154
184
217
242
269
307
329
360
391
461
130
200
250
300
350
400
450
500
m/z

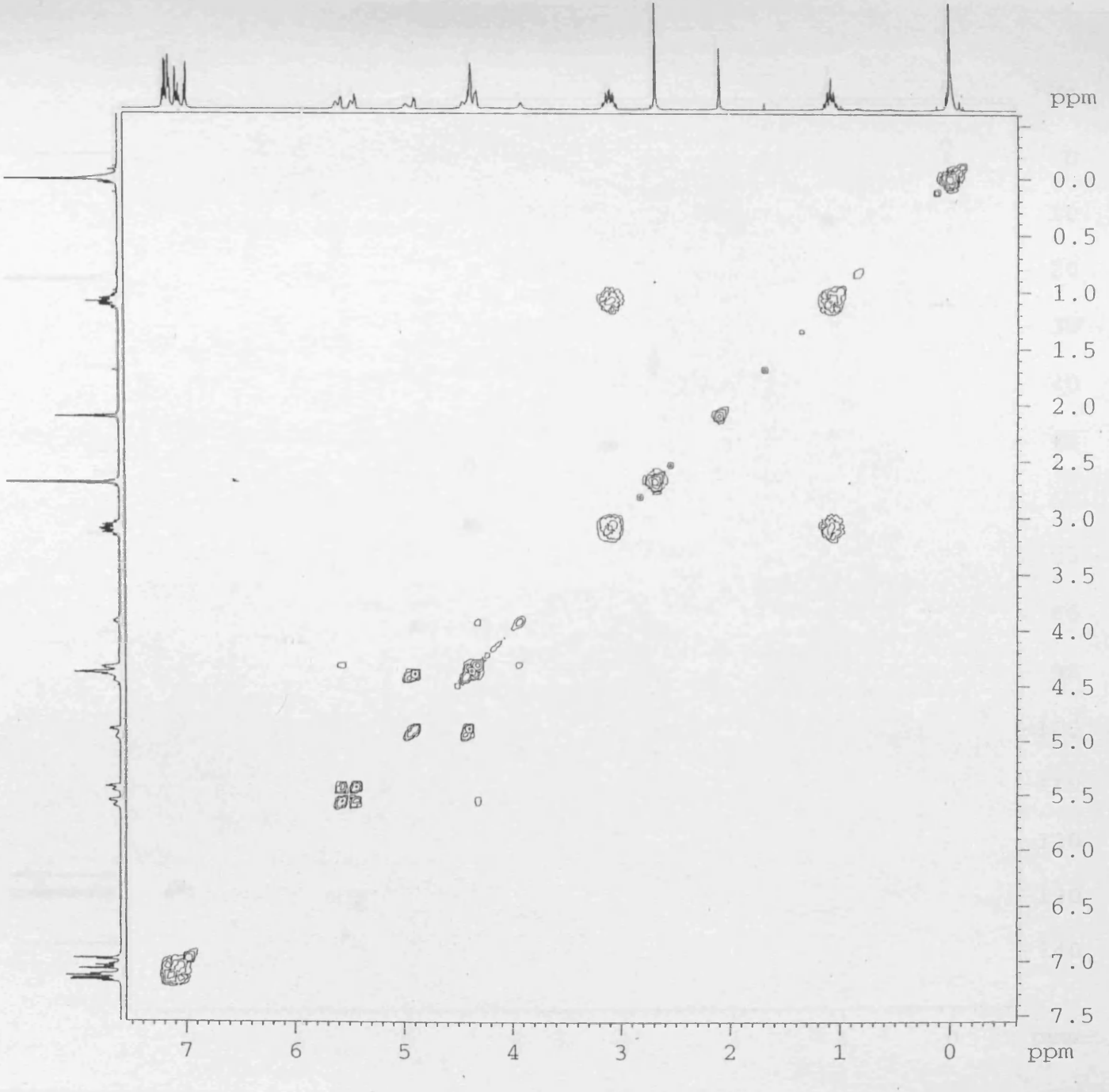
III-md-183
toluene-d8, 323K



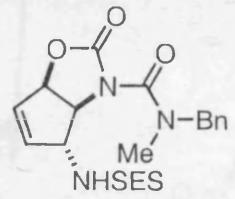

III-md-183
toluene-d8, 363K
O
O
N
O
N–Bn
Me
NHSES
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

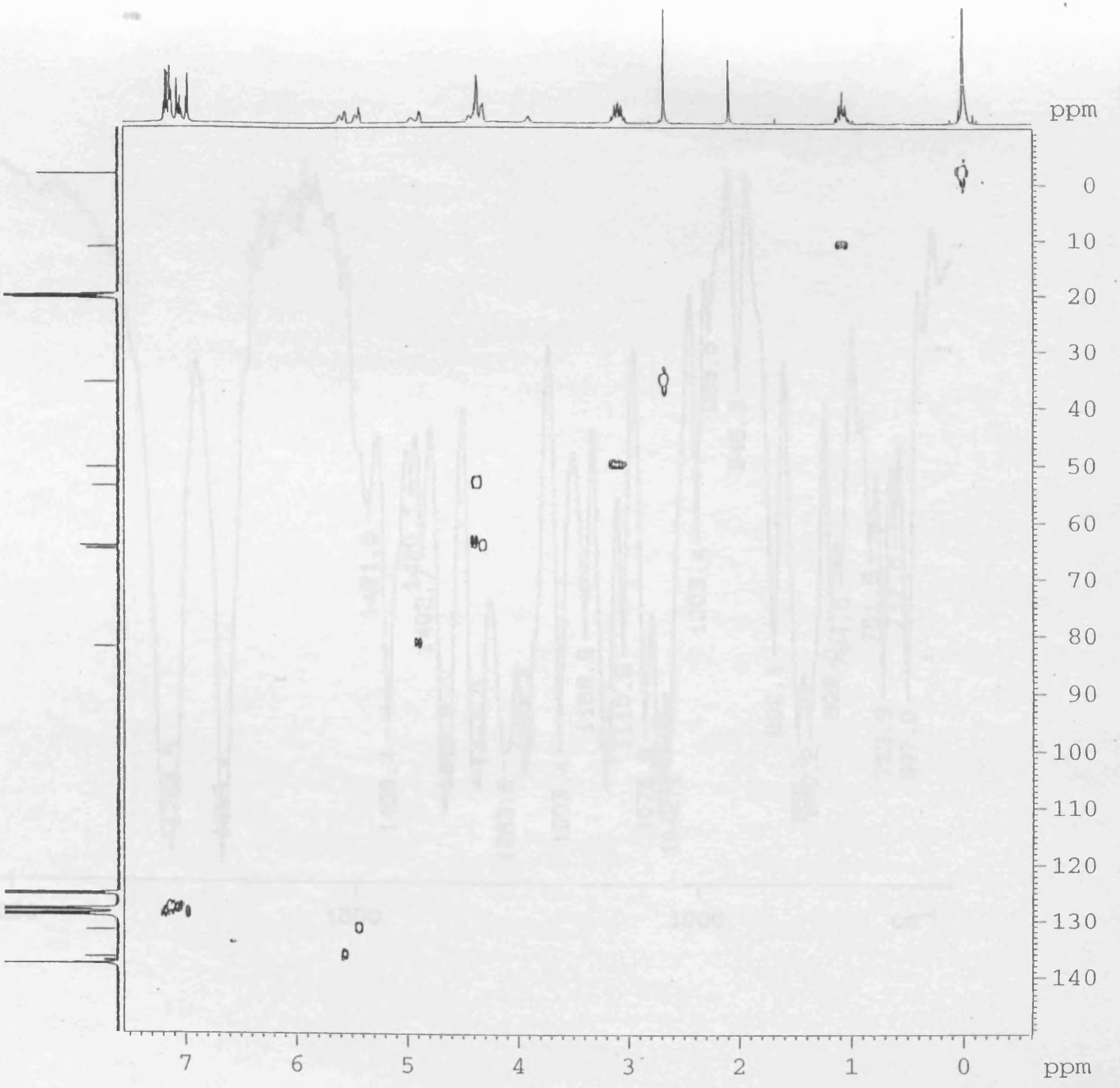
III-md-183
toluene-d8, 363 K
COSY

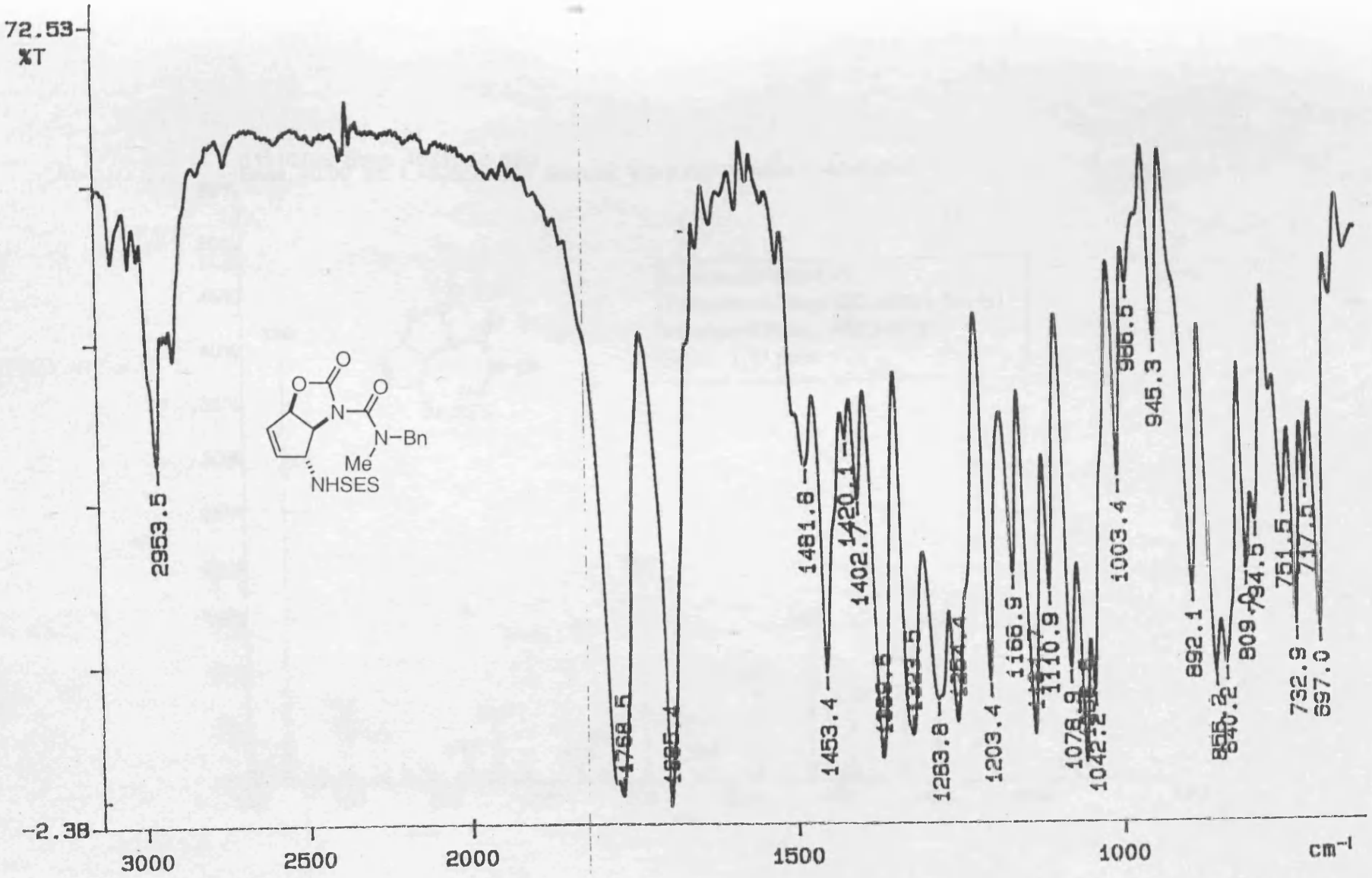


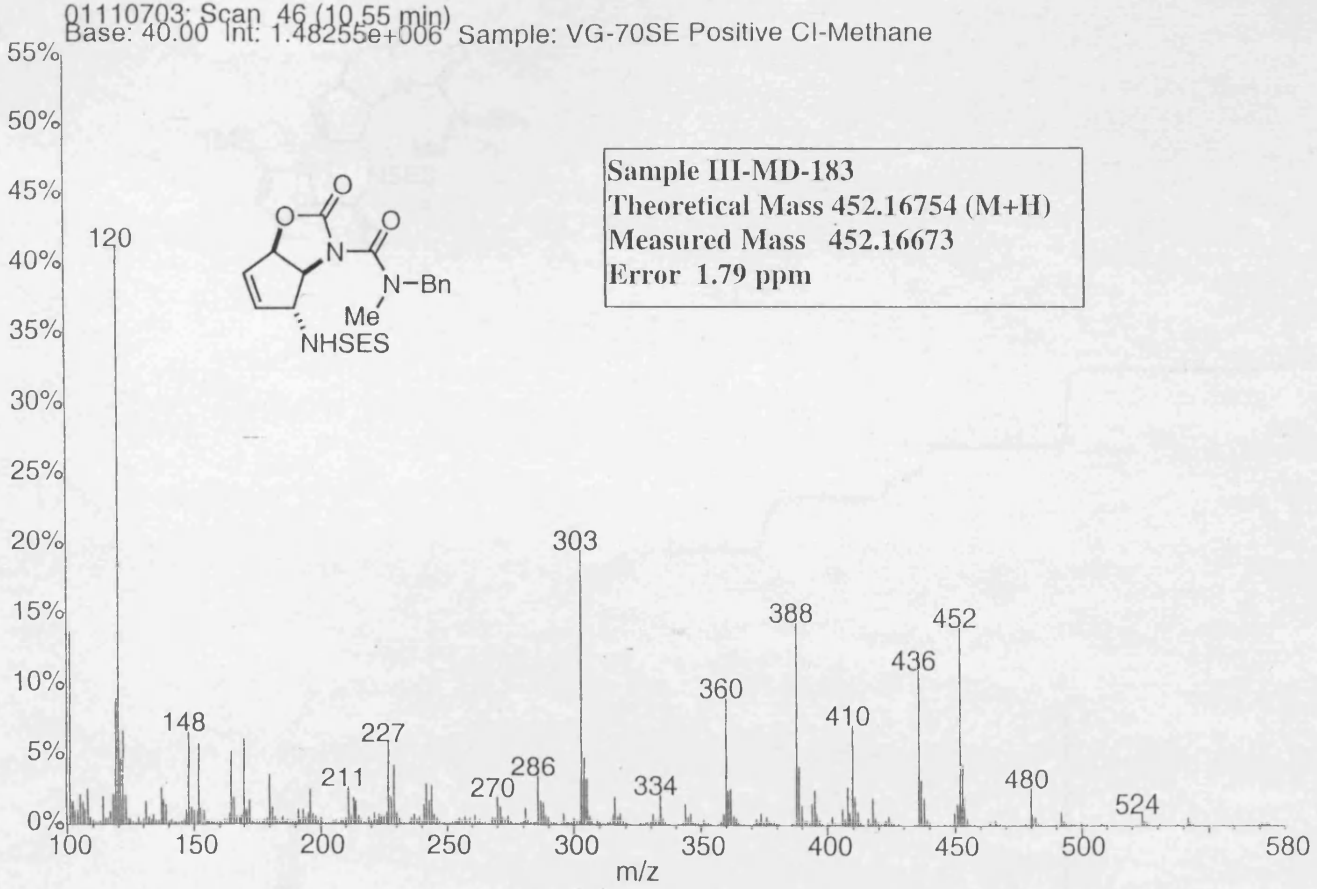


III-md-183
toluene-d8, 363K
HMQC

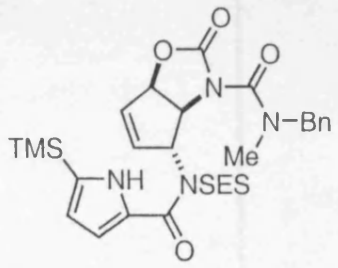




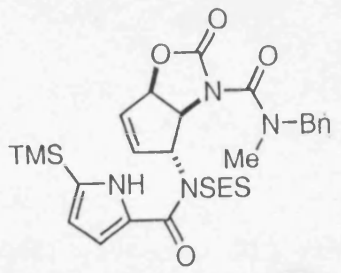

72.53
%T
-2.38
3000
2500
2000
1500
1000
cm-1
2953.5
1768.5
1685.4
1481.8
1453.4
1420.1
1402.7
1283.8
1203.4
1166.9
1110.9
1078.9
1042.2
1003.4
986.5
945.3
892.1
856.2
840.2
809.7
794.5
751.5
732.9
697.0
O
O
N
O
N–Bn
Me
NHSES


01110703: Scan 46 (10.55 min)
Base: 40.00 Int: 1.48255e+006 Sample: VG-70SE Positive CI-Methane
Sample III-MD-183
Theoretical Mass 452.16754 (M+H)
Measured Mass 452.16673
Error 1.79 ppm
N–Bn
Me
NHSES
55%
50%
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
120
148
211
227
270
286
303
334
360
388
410
436
452
480
524
100
150
200
250
300
350
400
450
500
580
m/z

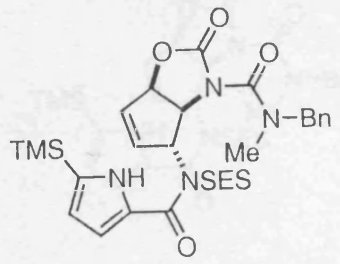
IV-md-28
C6D6, 343 K

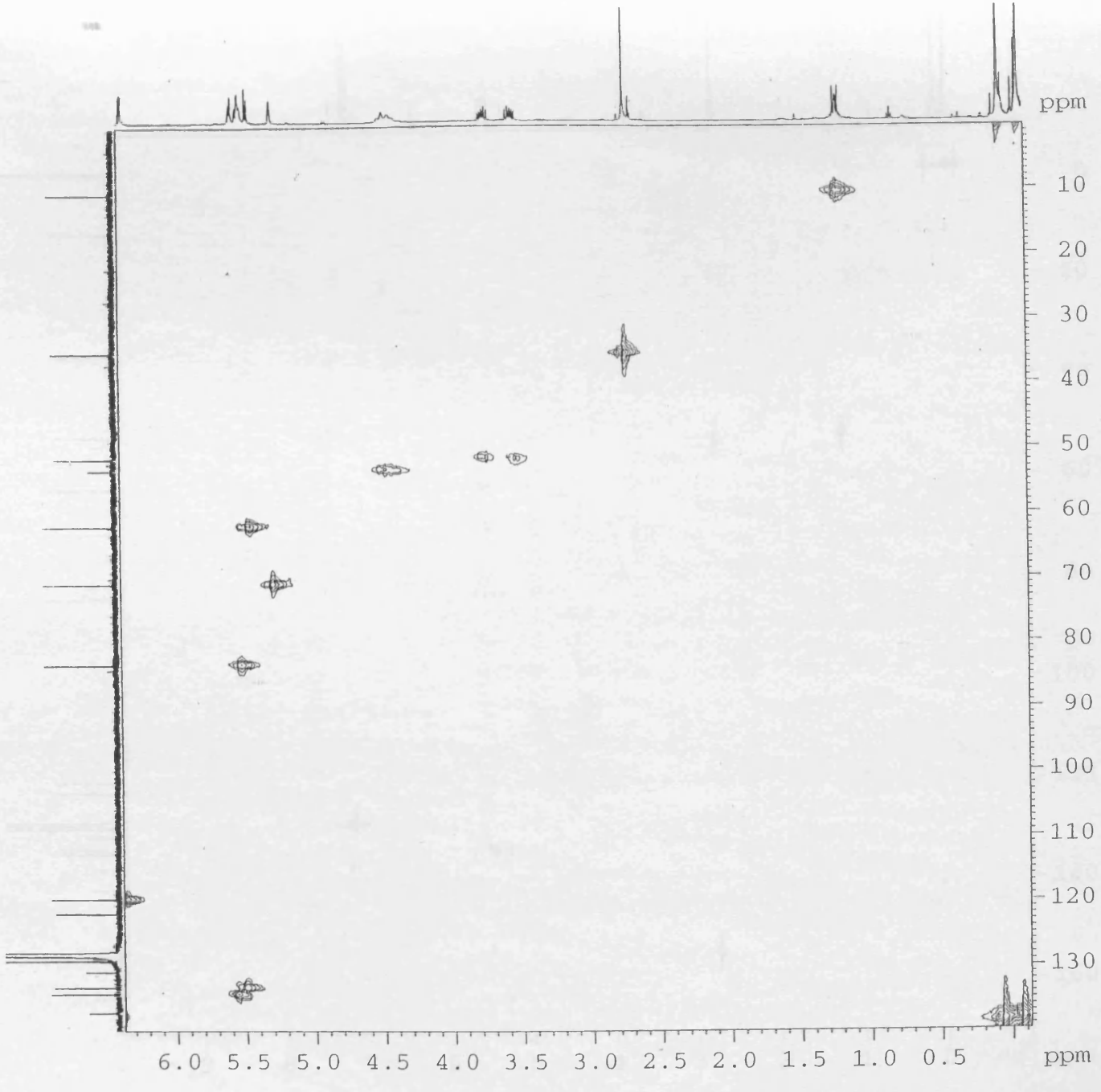


IV-md-28
C6D6, 343 K

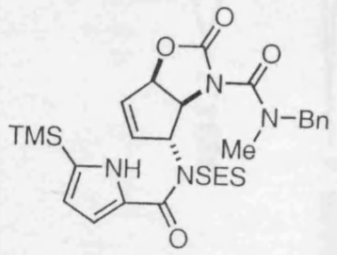


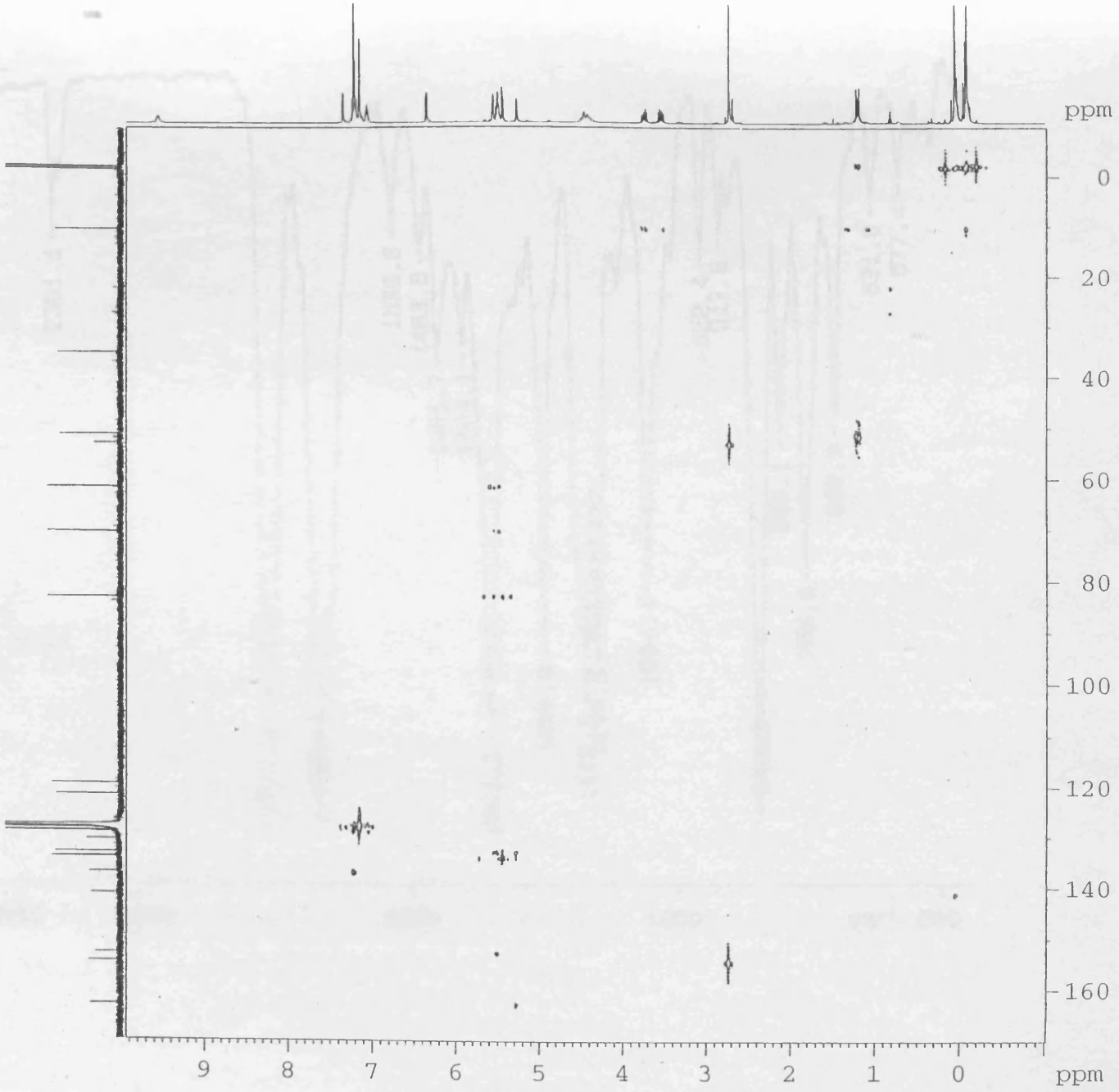
IV-md-28
C6D6, 343 K
HMQC

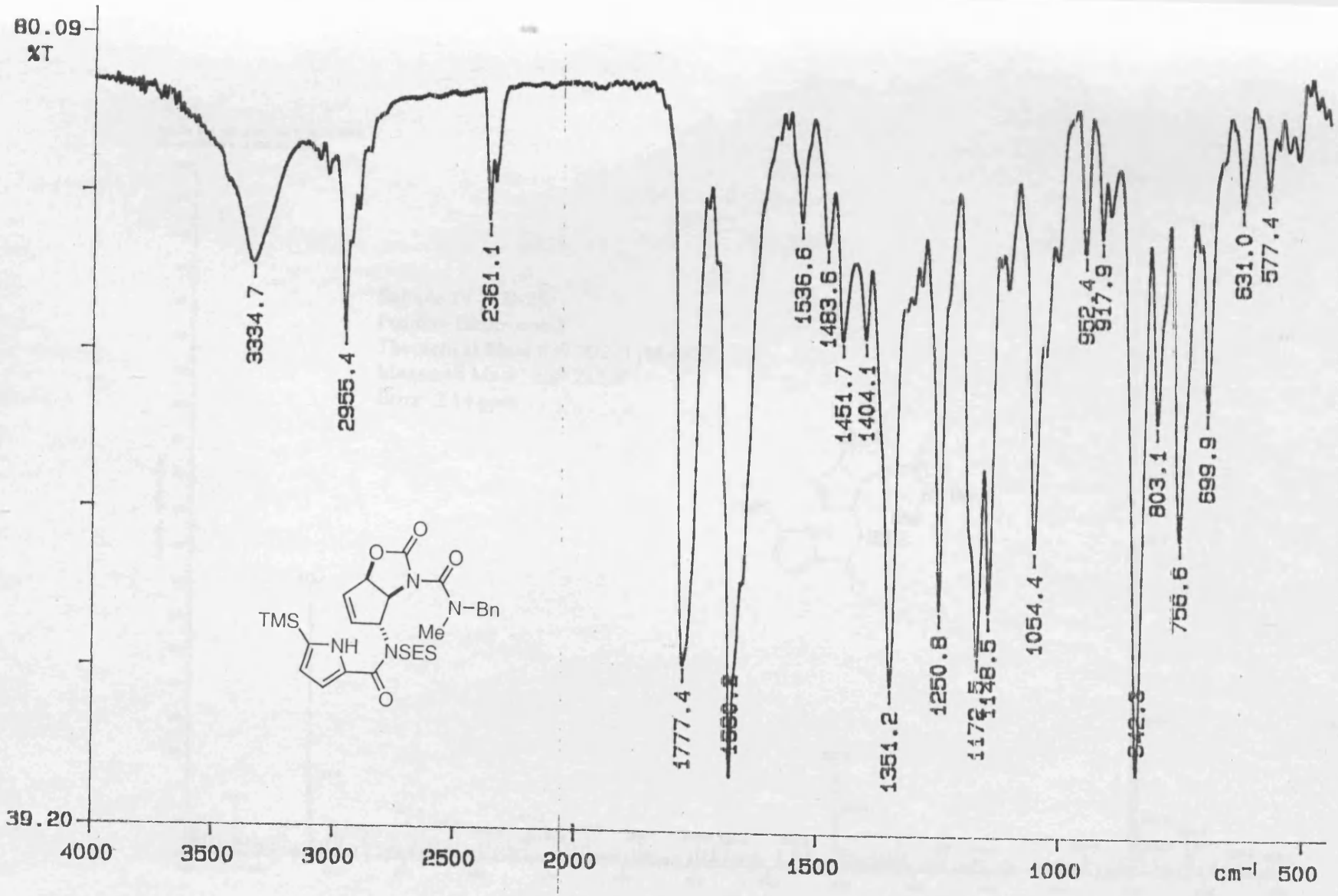


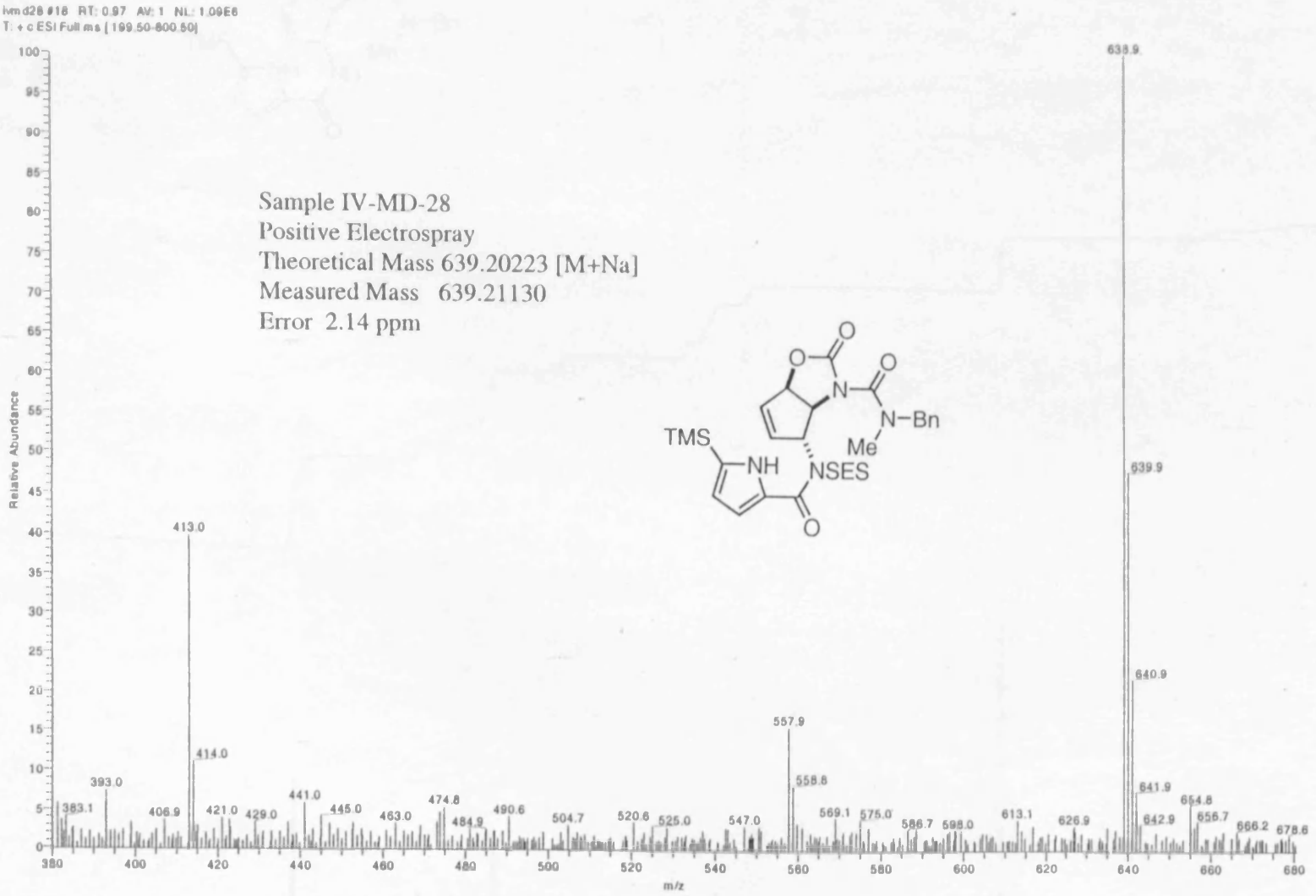


IV-md-28
C6D6, 348K
hmbc

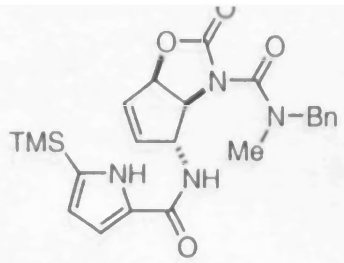




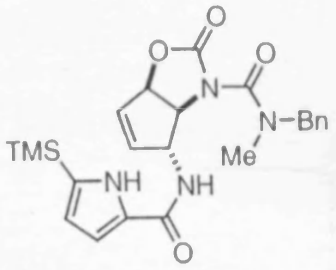

80.09
%T
39.20
3334.7
2955.4
2361.1
1777.4
1536.6
1483.6
1451.7
1404.1
1351.2
1250.8
1148.5
1054.4
952.4
917.9
803.1
756.6
699.9
631.0
577.4
4000
3500
3000
2500
2000
1500
1000
cm-1
500
TMS
NH
NSES
Me
N-Bn
O
N


lvmd28 #18 RT: 0.97 AV: 1 NL: 1.09E6
T: + c ESI Full ms [199.50-800.50]
Sample IV-MD-28
Positive Electrospray
Theoretical Mass 639.20223 [M+Na]
Measured Mass 639.21130
Error 2.14 ppm
TMS
NH
NSES
Me
N–Bn
Relative Abundance
m/z
639.9
640.9
641.9
642.9
413.0
414.0
393.0
383.1
406.9
421.0
429.0
441.0
445.0
463.0
474.8
484.9
490.6
504.7
520.6
525.0
547.0
557.9
558.8
569.1
575.0
586.7
598.0
613.1
626.9
654.8
656.7
666.2
678.6

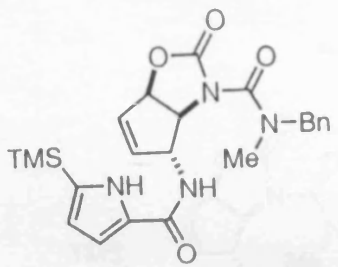
IV-md-45
CDCl3, 328 K

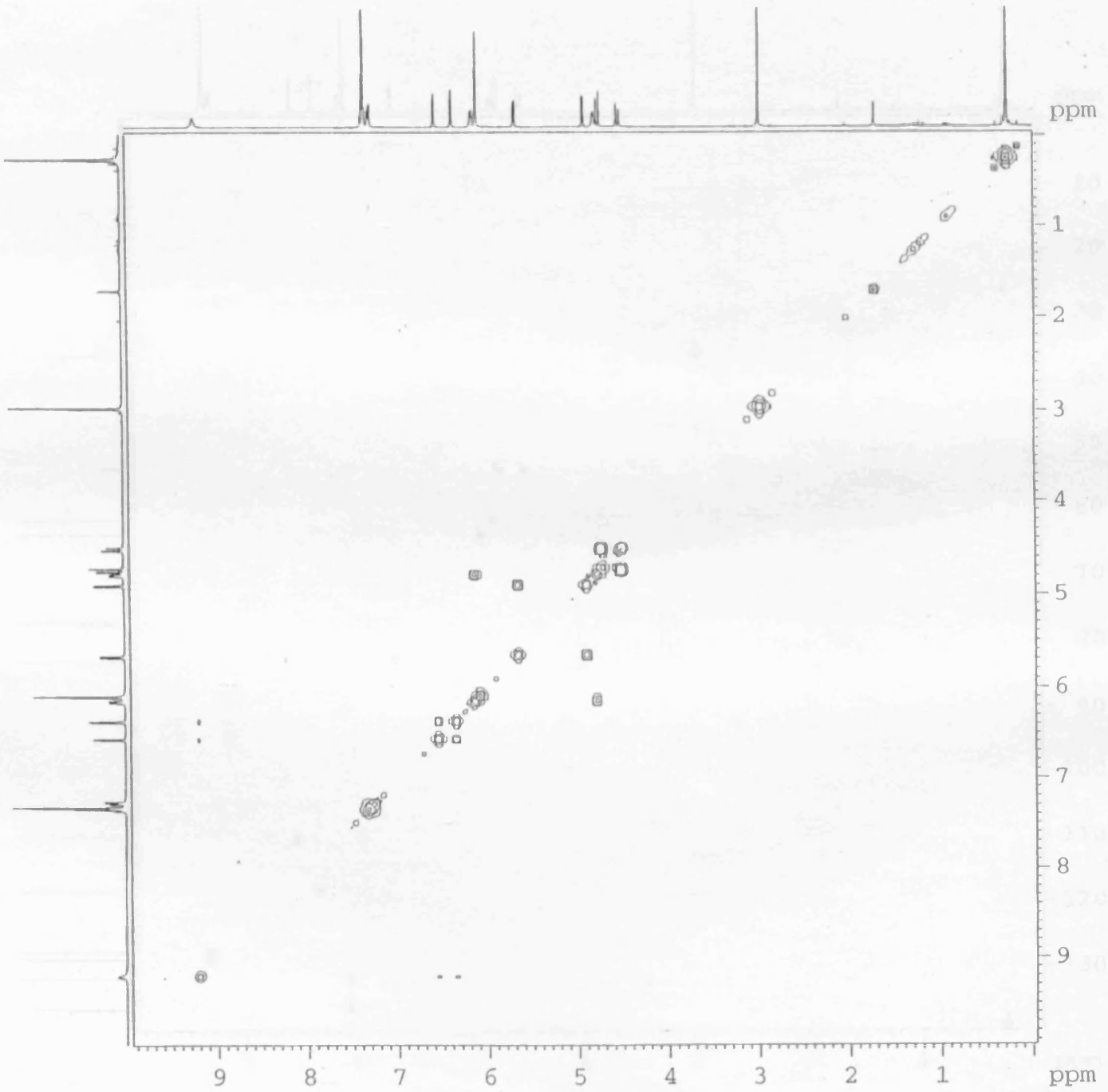


IV-md-45
CDCl3, 328 K

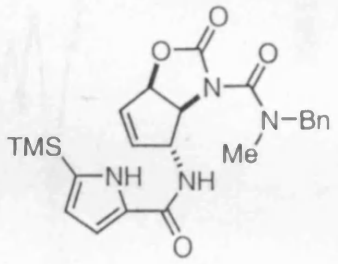


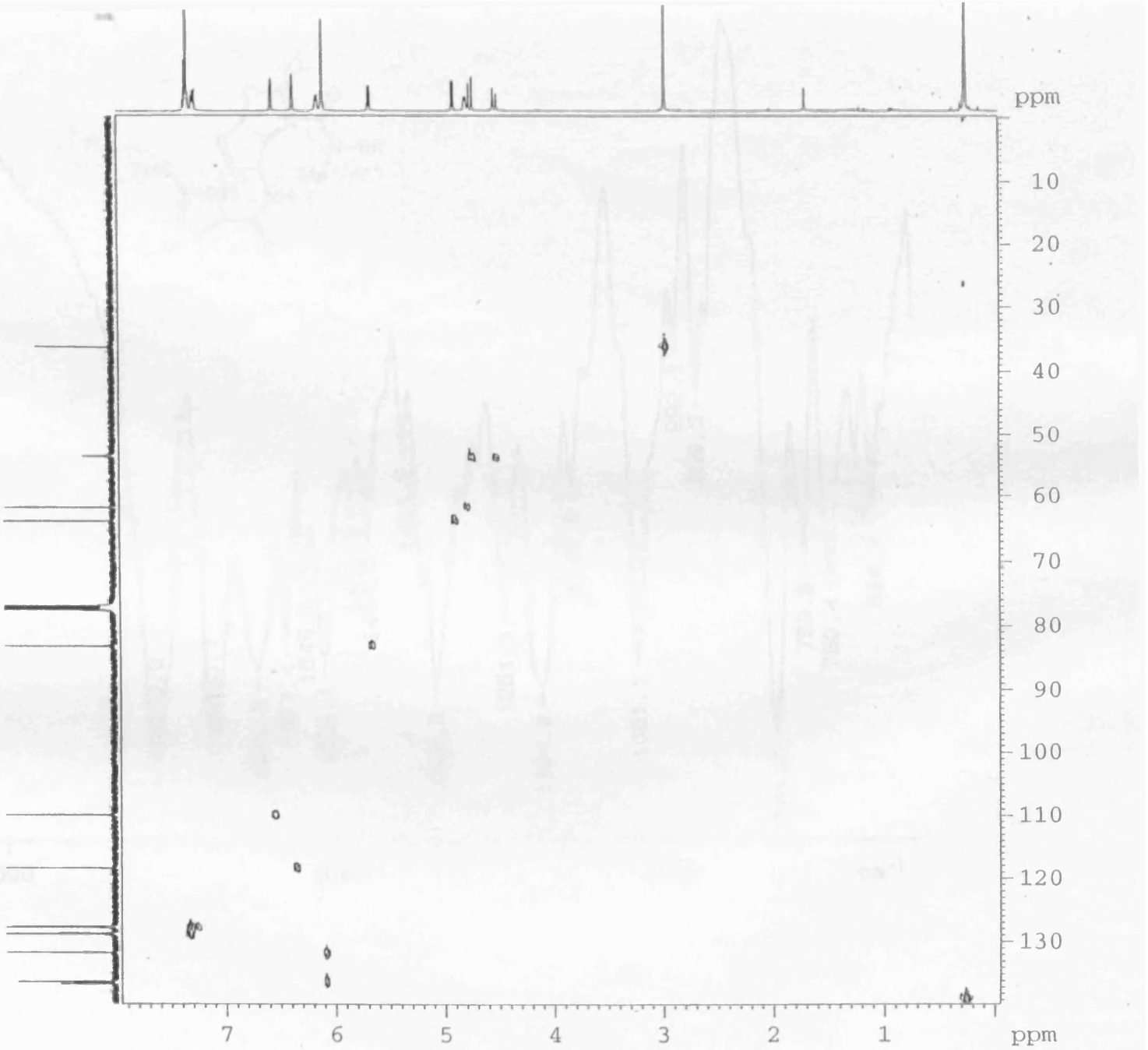
IV-md-45
CDCl3, 328 K
COSY

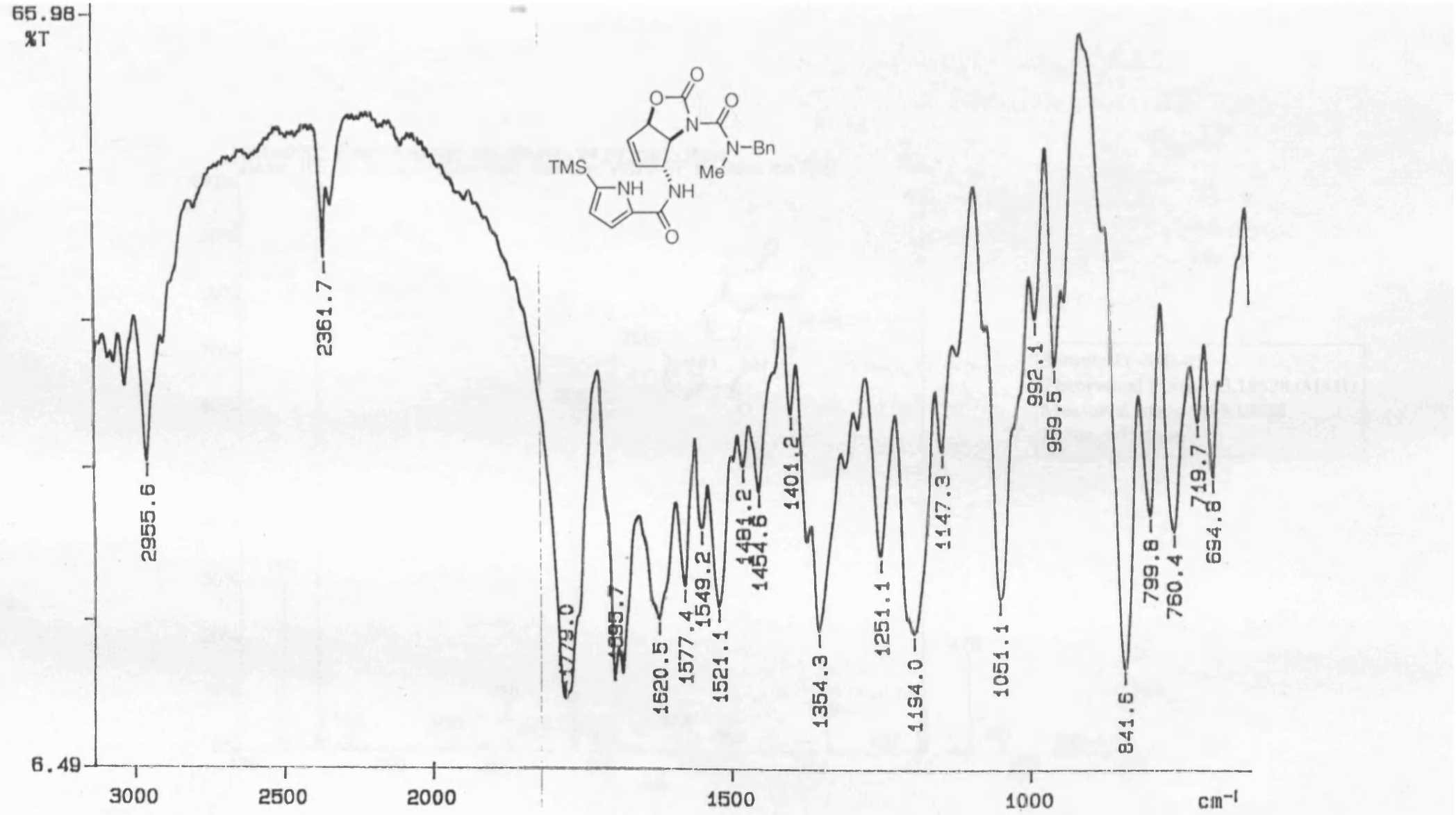


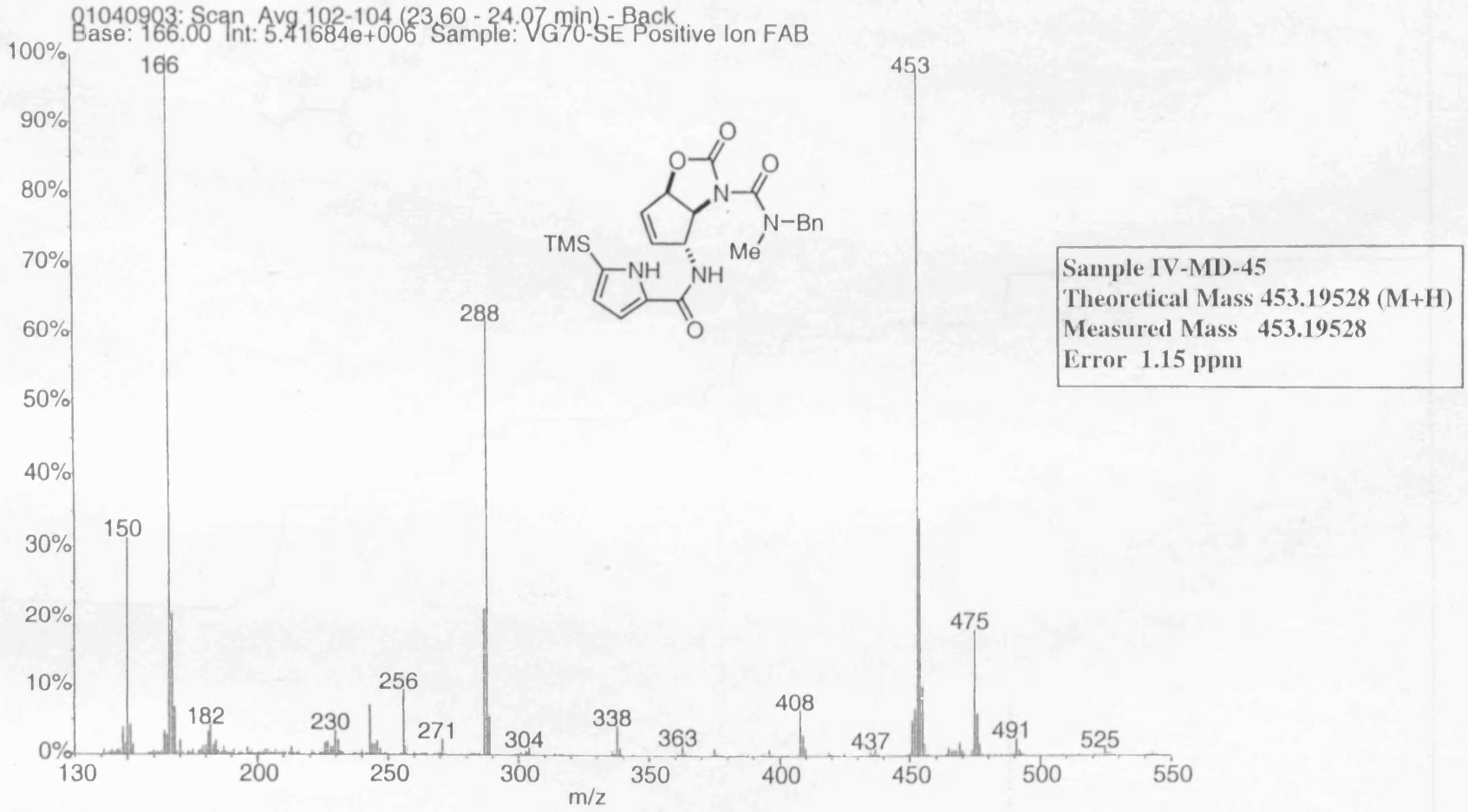


IV-md-45
CDCl3, 328 K
HMQC

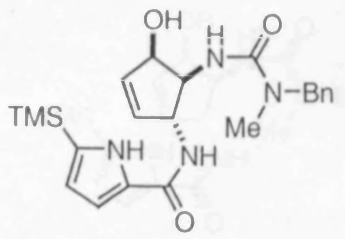




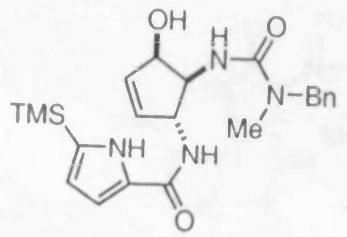

65.98
%T
6.49
3000
2500
2000
1500
1000
cm-1
2955.6
2361.7
1779.0
1695.7
1620.5
1577.4
1549.2
1521.1
1481.2
1454.8
1401.2
1354.3
1251.1
1194.0
1147.3
1051.1
992.1
959.5
841.6
799.8
760.4
719.7
694.8
TMS
NH
NH
N
O
O
O
O
N-Bn
Me


01040903: Scan Avg 102-104 (23.60 - 24.07 min) - Back
Base: 166.00 Int: 5.41684e+006 Sample: VG70-SE Positive Ion FAB
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
166
453
288
150
182
230
256
271
304
338
363
408
437
475
491
525
130
200
250
300
350
400
450
500
550
m/z
TMS
NH
NH
O
O
O
N
N–Bn
Me
O
Sample IV-MD-45
Theoretical Mass 453.19528 (M+H)
Measured Mass 453.19528
Error 1.15 ppm

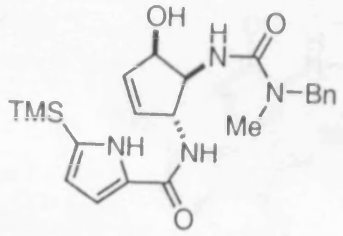
IV-md-46
CDCl3, 298 K



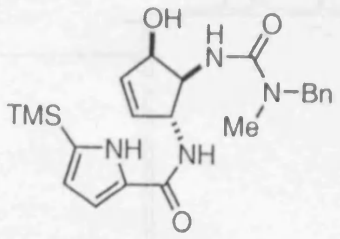
IV-md-46
CDCl3, 298 K



IV-md-46
CDCl3, 298 K

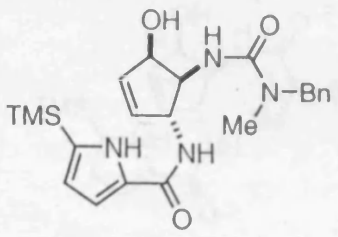


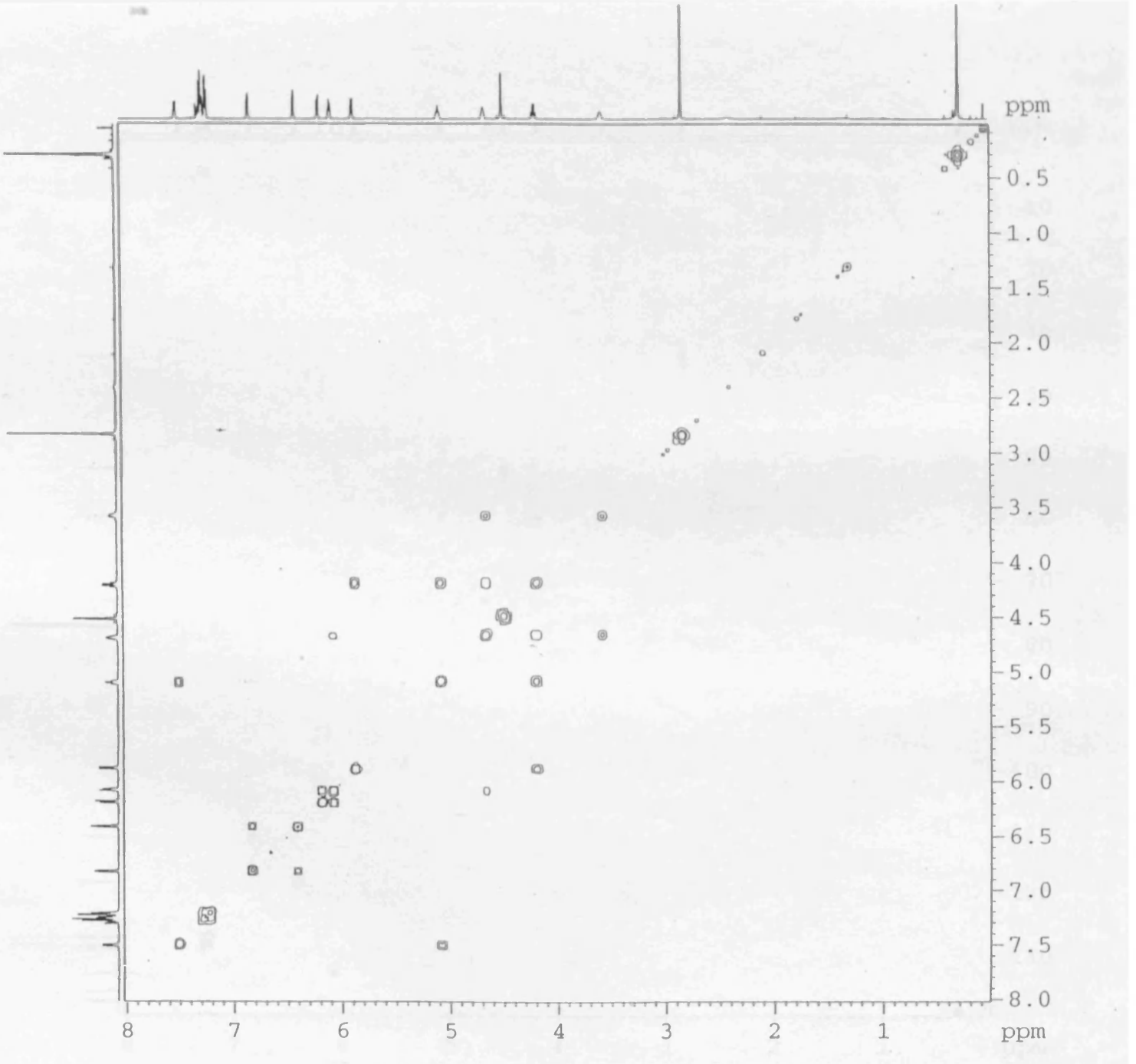
IV-md-46
CDCl3, 298 K
DEPT



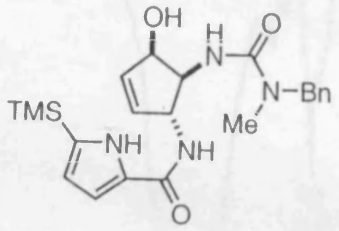
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

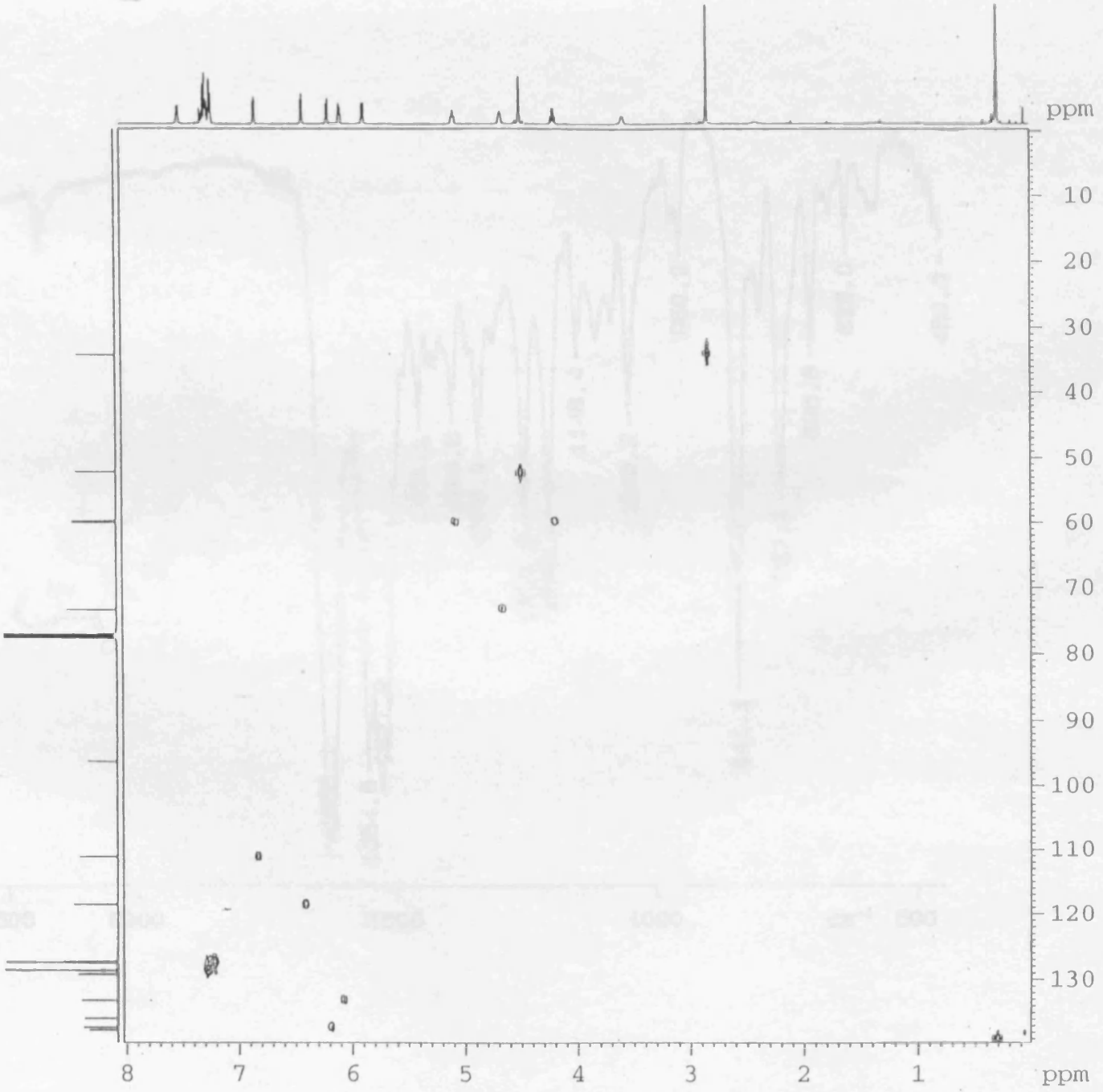
IV-md-46
CDCl3, 298 K
COSY

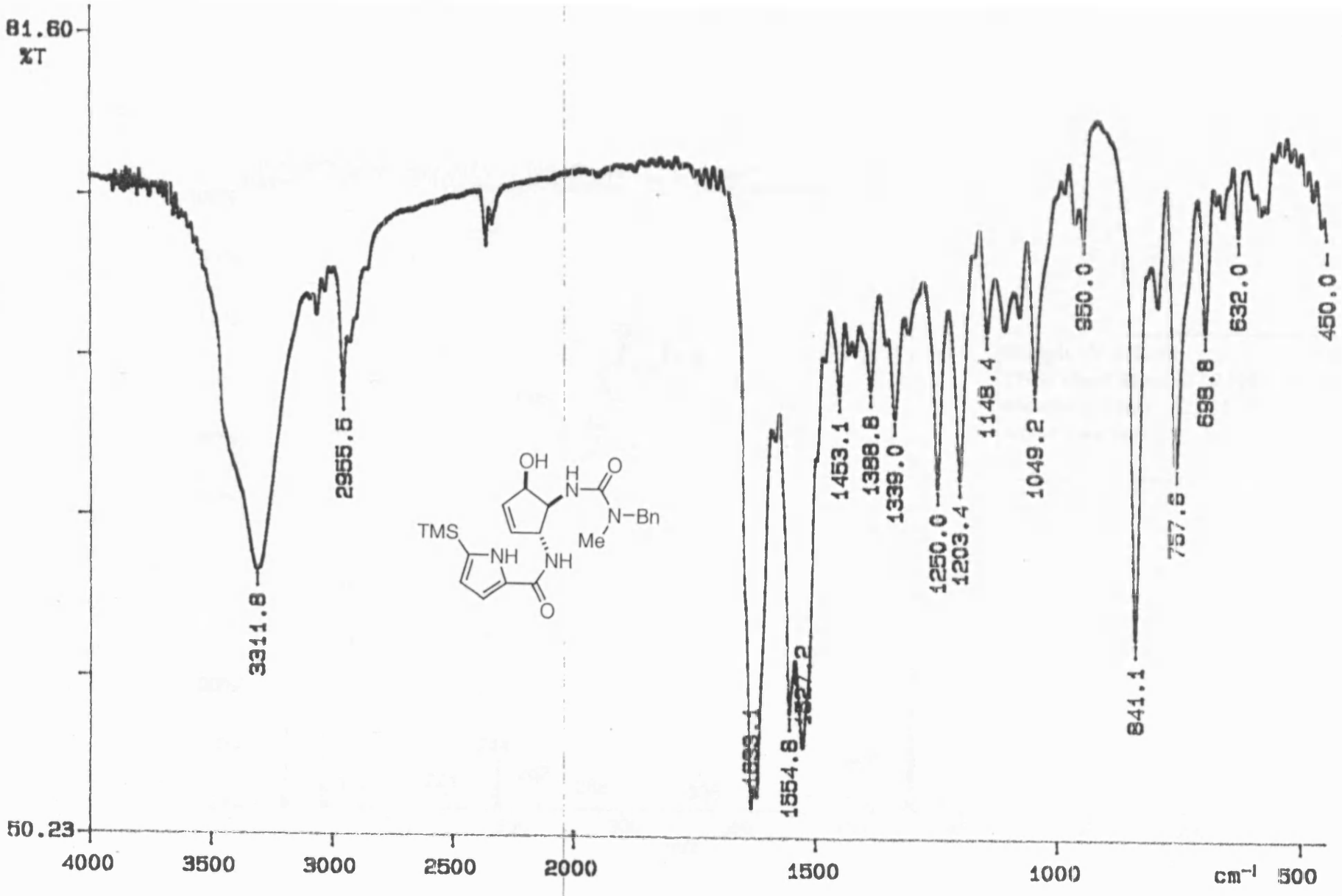


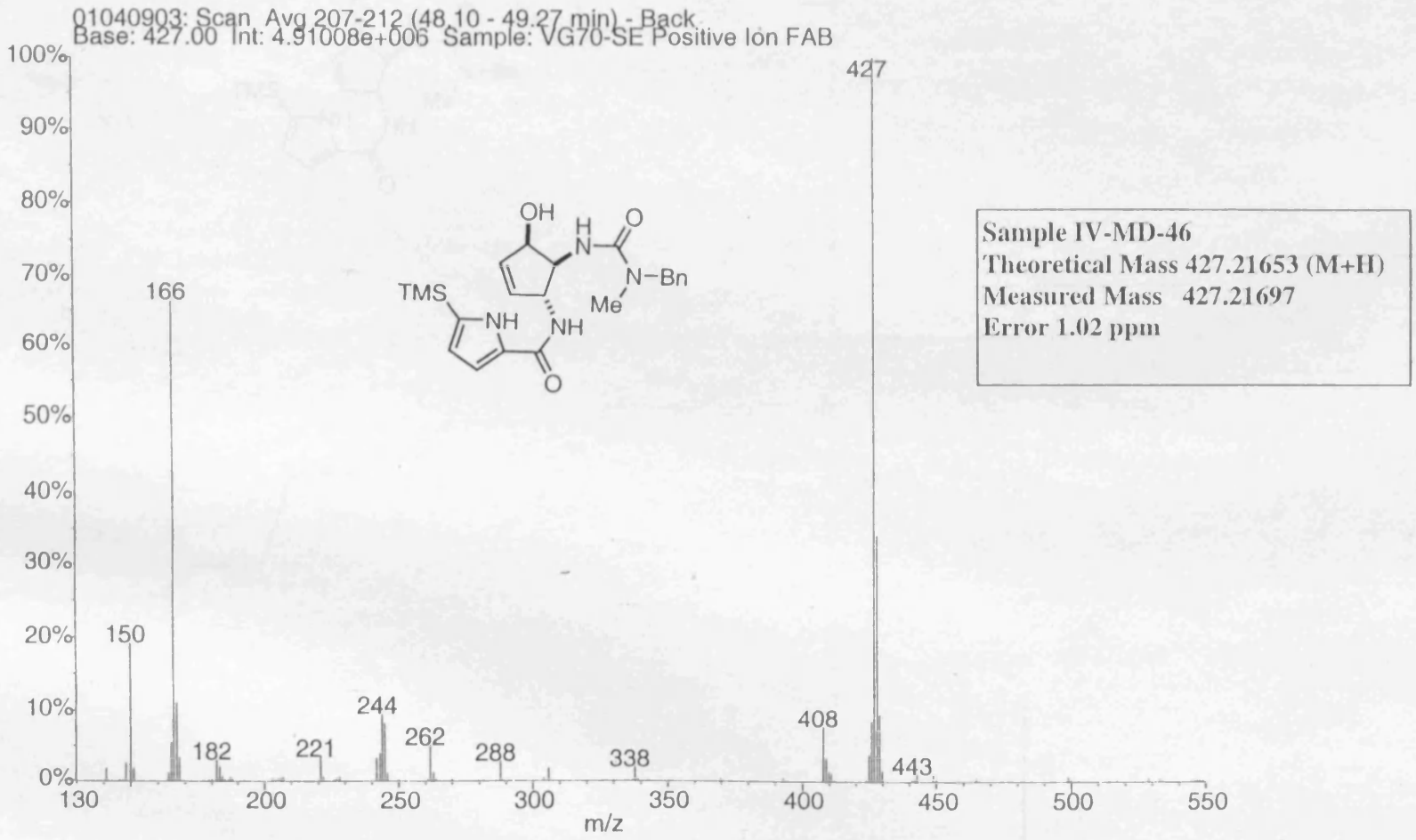


IV-md-46
CDCl3, 298 K
HMQC

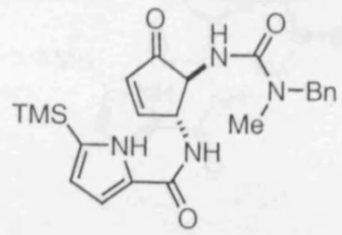




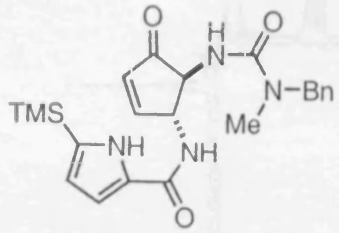

81.60
%T
50.23
3311.8
2955.5
1633.1
1554.8
1327.2
1453.1
1388.8
1339.0
1250.0
1203.4
1148.4
1049.2
950.0
841.1
757.6
698.8
632.0
450.0
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
500
OH
N
H
O
N–Bn
Me
TMS
NH
NH
O


01040903: Scan Avg 207-212 (48.10 - 49.27 min) - Back
Base: 427.00 Int: 4.91008e+006 Sample: VG70-SE Positive Ion FAB
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
130
200
250
300
350
400
450
500
550
m/z
427
166
150
182
221
244
262
288
338
408
443
OH
H
N
O
N–Bn
Me
TMS
NH
NH
O
Sample IV-MD-46
Theoretical Mass 427.21653 (M+H)
Measured Mass 427.21697
Error 1.02 ppm

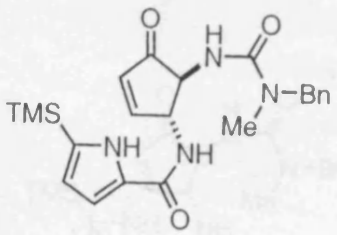
IV-md-50
CDCl3, 298 K

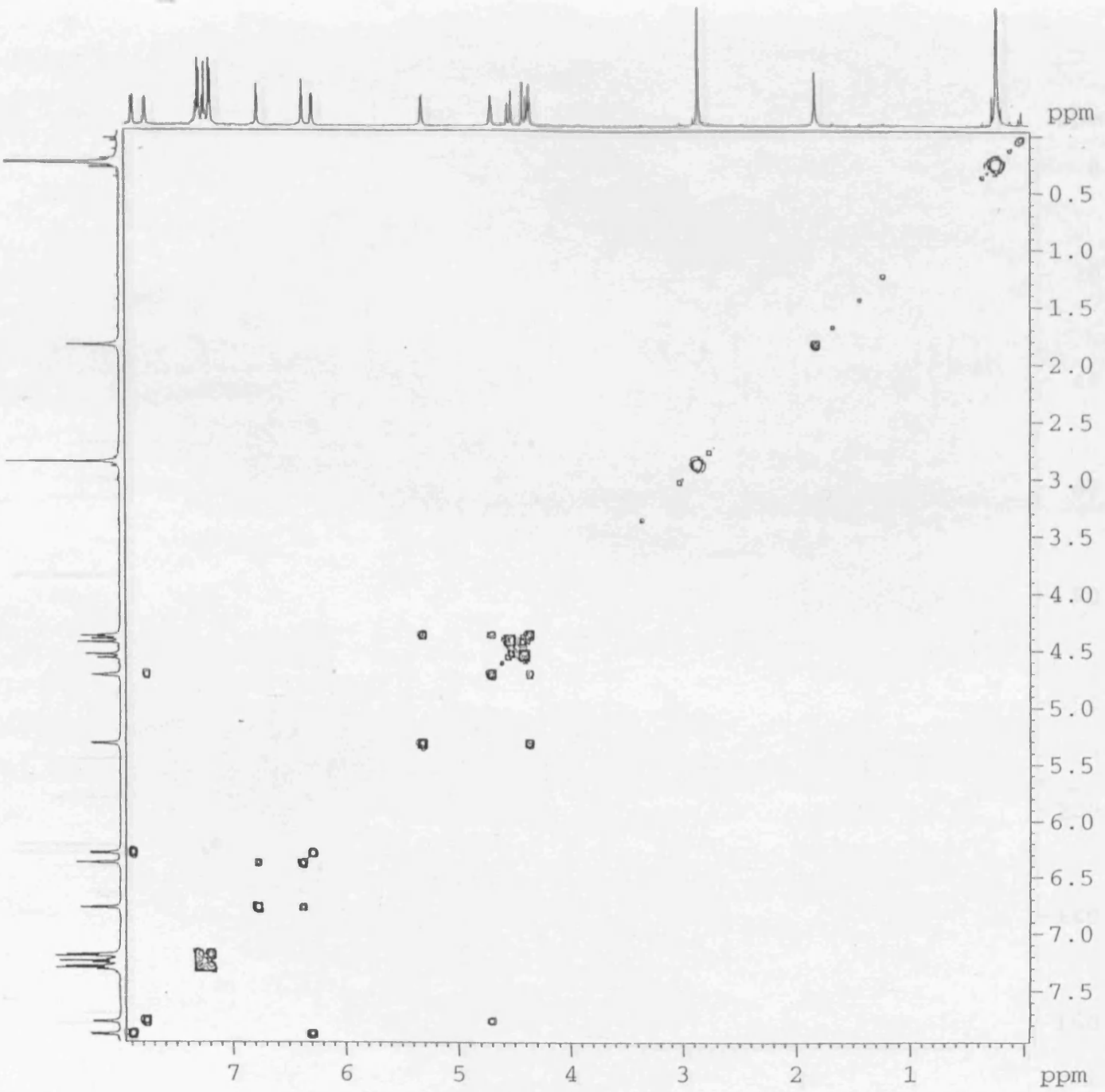


IV-md-50
CDCl3, 298 K

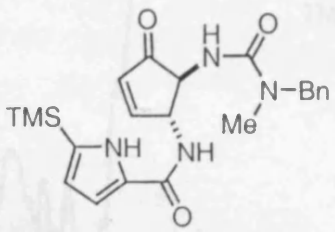


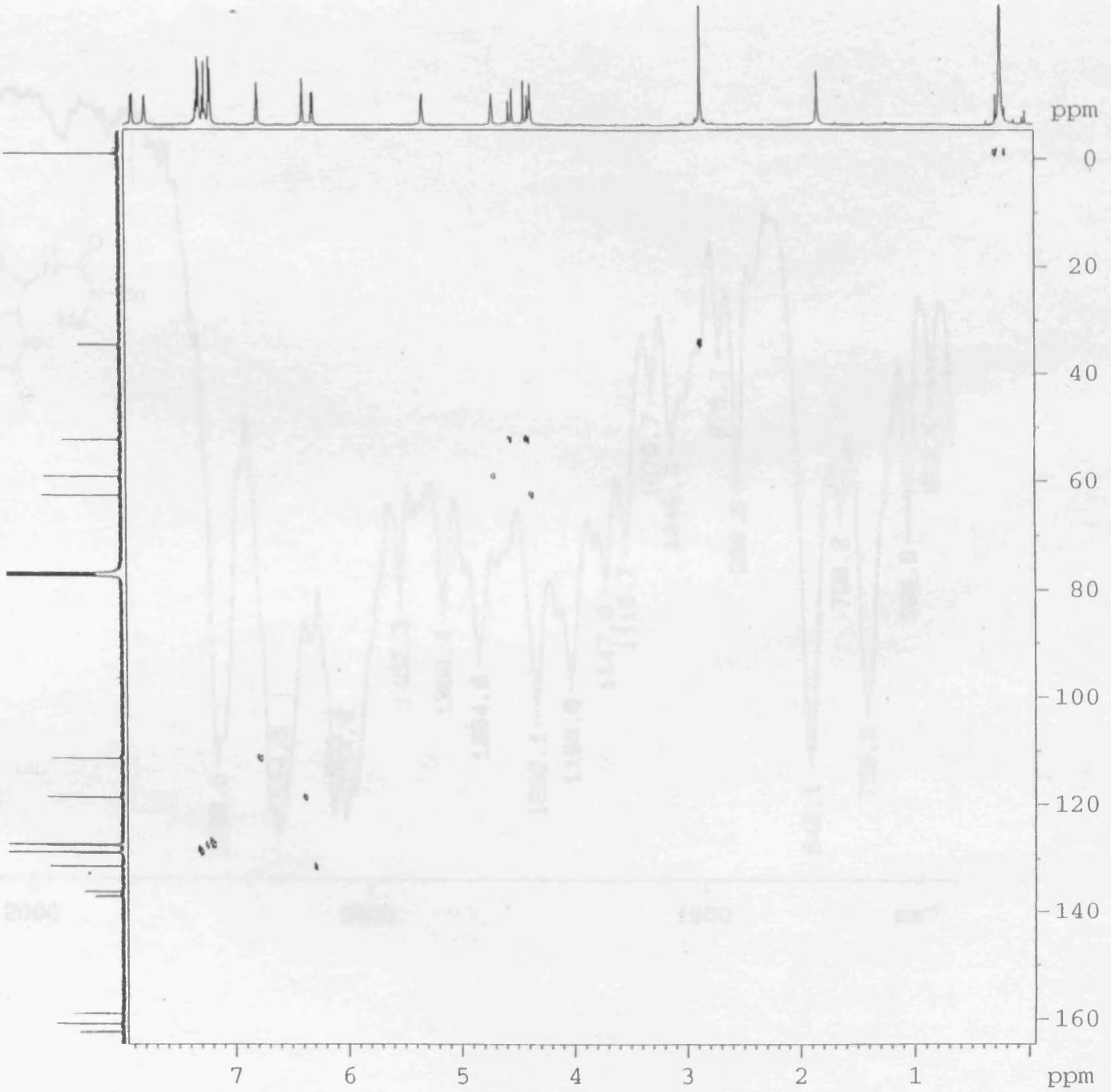
IV-md-50
CDCl3, 298 K
COSY

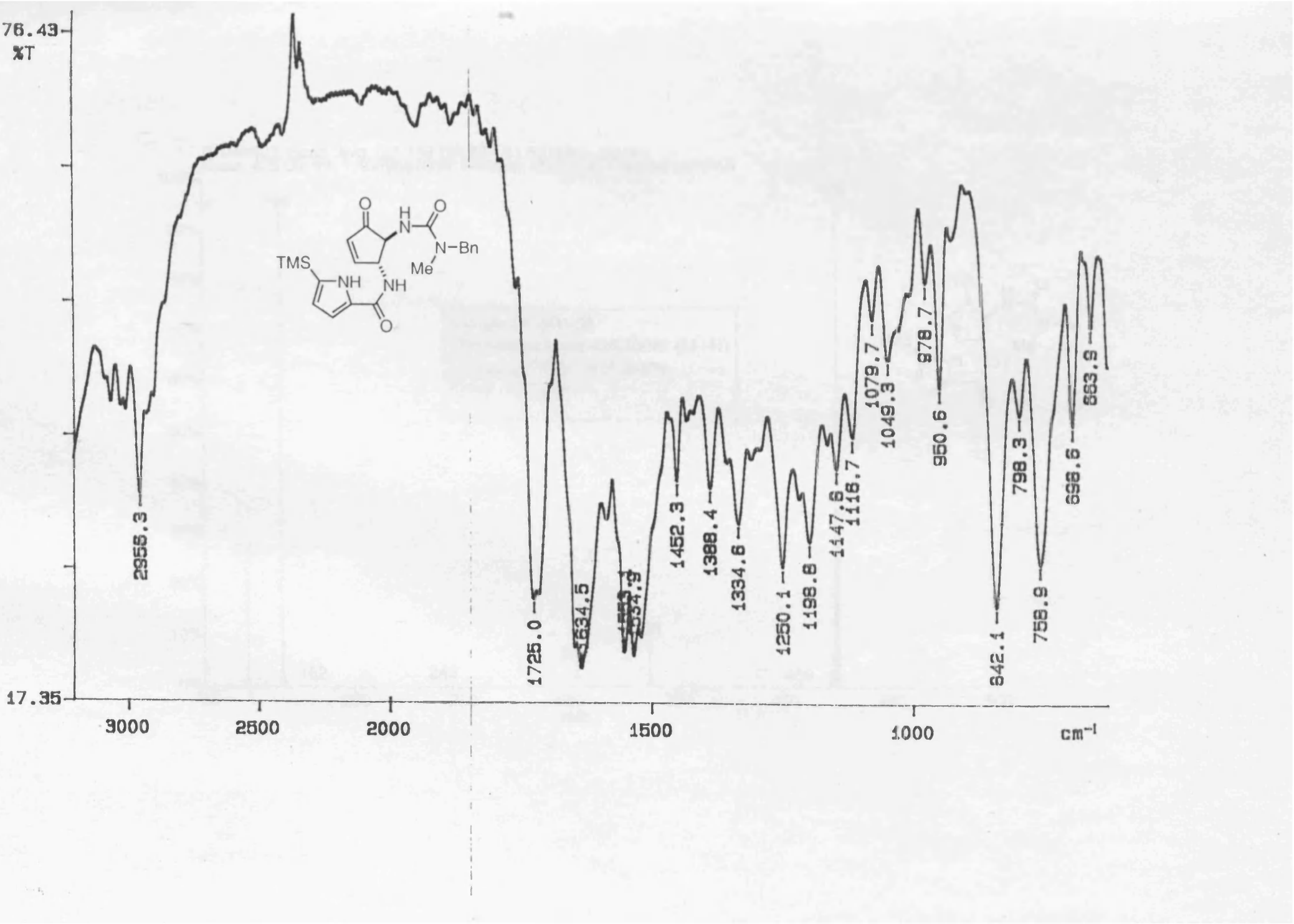


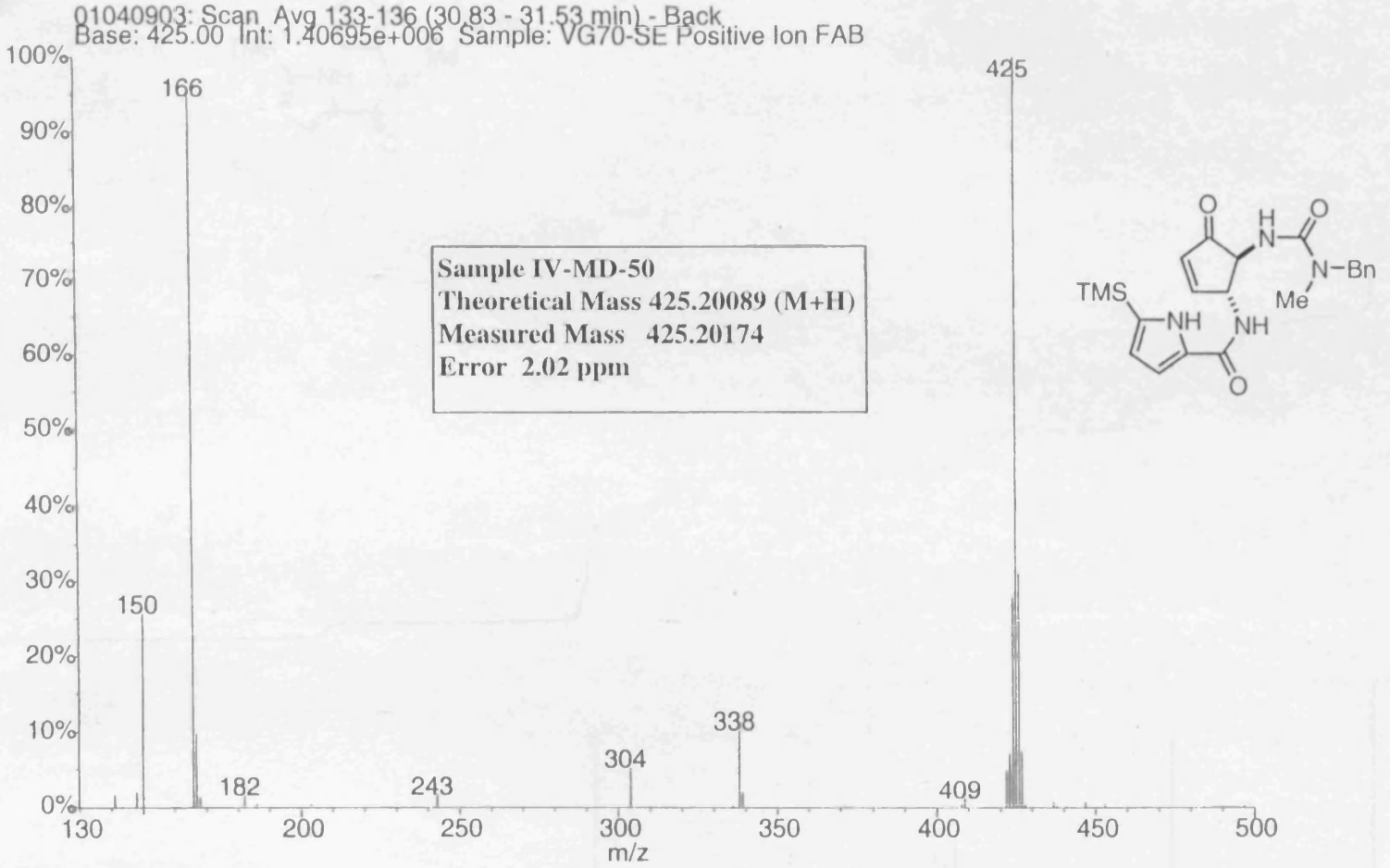


IV-md-50
CDCl3, 298 K
HMQC

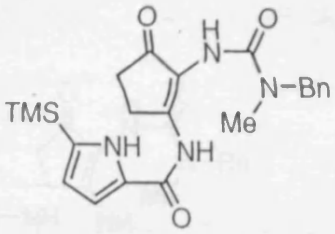




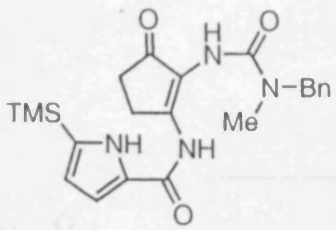

76.43
%T
17.35
2958.3
1725.0
1634.5
1452.3
1388.4
1334.6
1250.1
1198.8
1147.6
1118.7
1079.7
1049.3
978.7
950.6
842.1
798.3
758.9
698.6
663.9
3000
2500
2000
1500
1000
cm-1
TMS
NH
NH
N-Bn
Me


01040903: Scan Avg 133-136 (30.83 - 31.53 min) - Back
Base: 425.00 Int: 1.40695e+006 Sample: VG70-SE Positive Ion FAB
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
166
425
150
182
243
304
338
409
130
200
250
300
350
400
450
500
m/z
Sample IV-MD-50
Theoretical Mass 425.20089 (M+H)
Measured Mass 425.20174
Error 2.02 ppm
TMS
NH
NH
H
N
O
O
N–Bn
Me
O
O

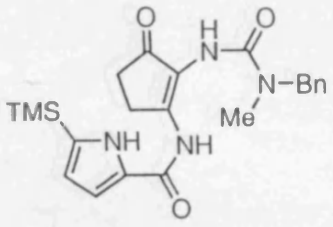
IV-md-16a
CDCl3, 298 K

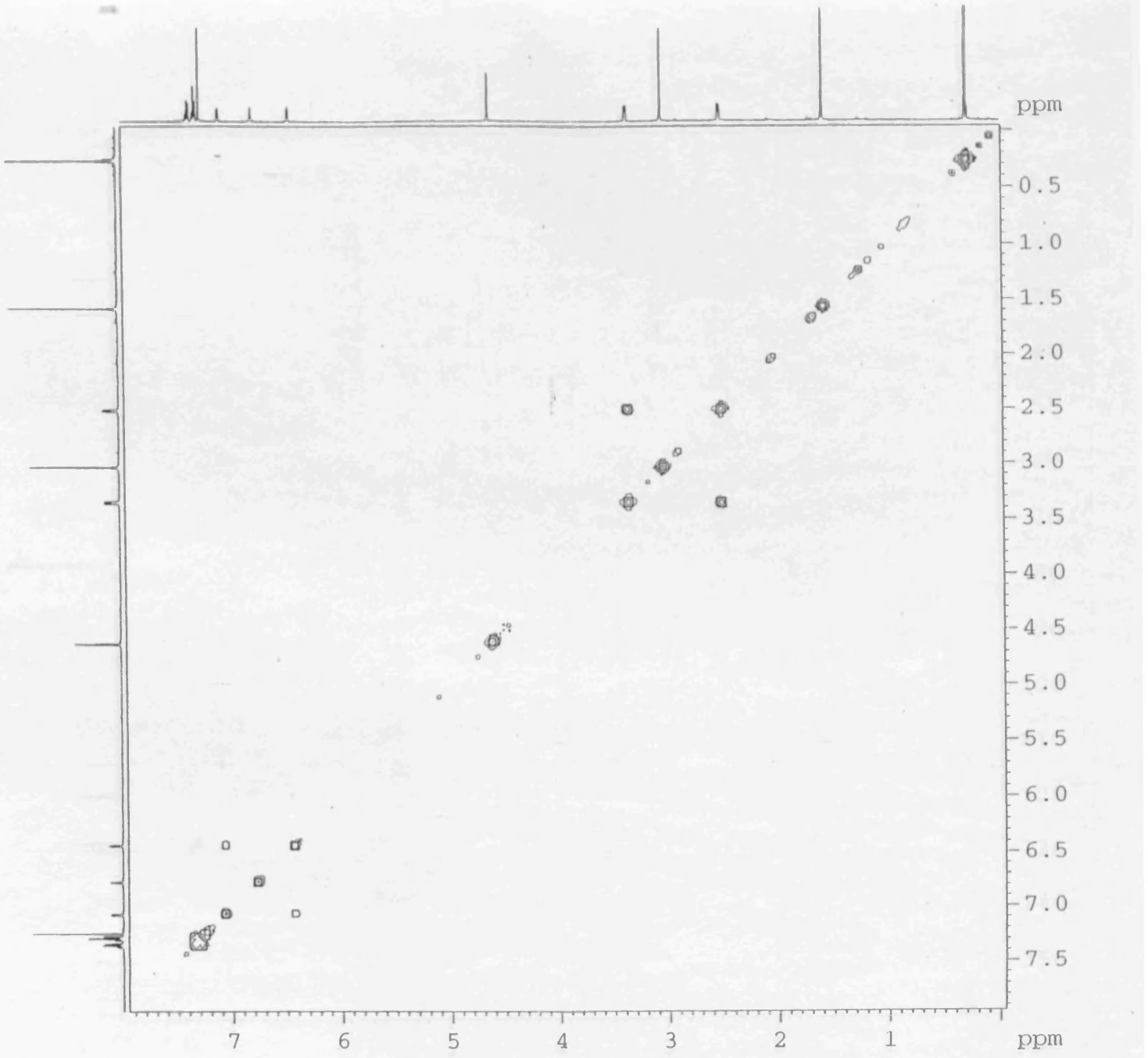


IV-md-16a
CDCl3, 298 K

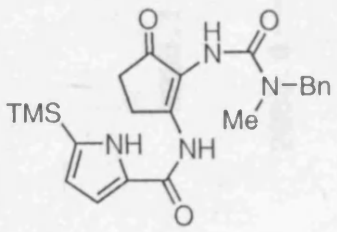


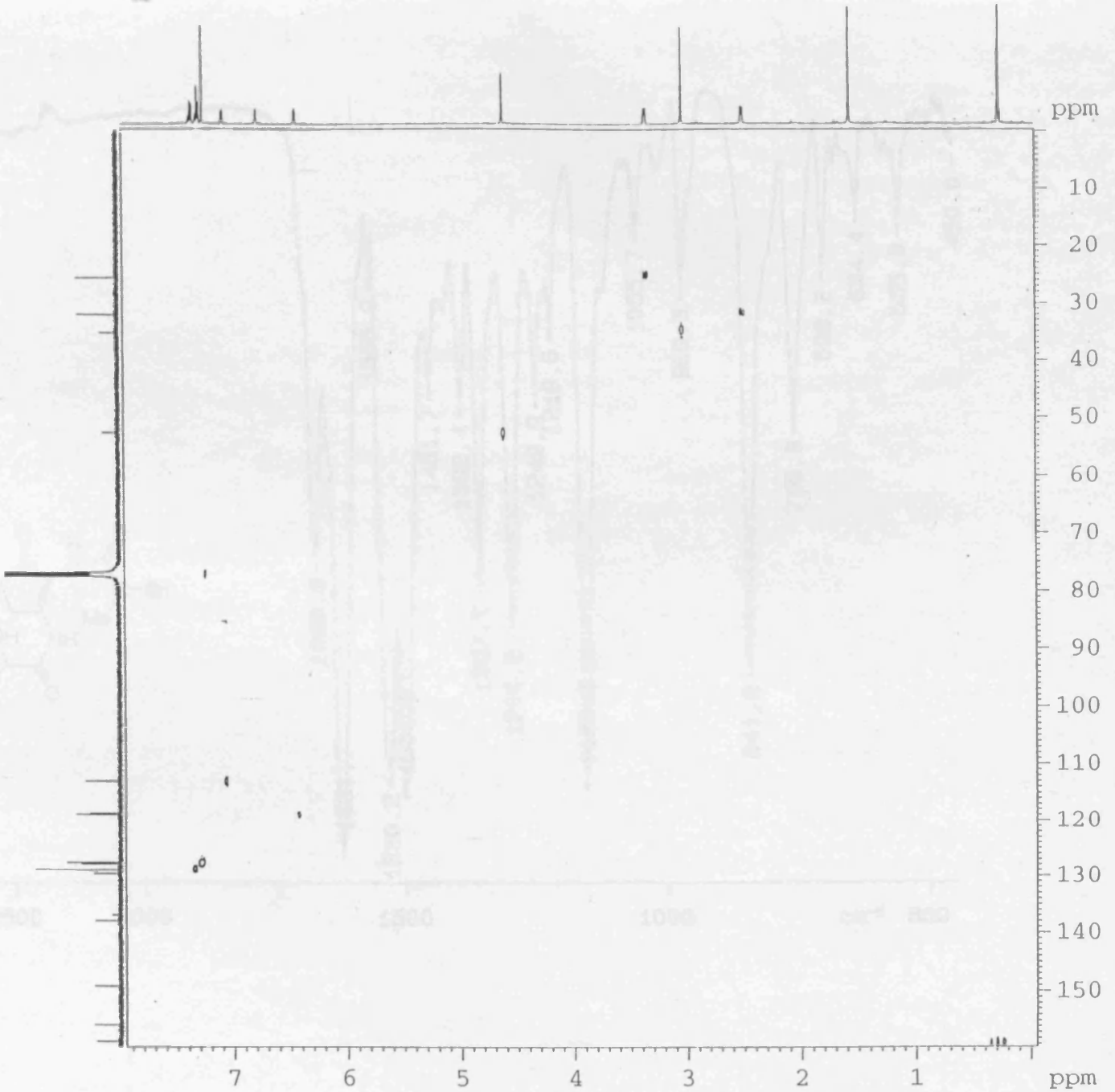
IV-md-16a
CDCl3, 298 K
COSY

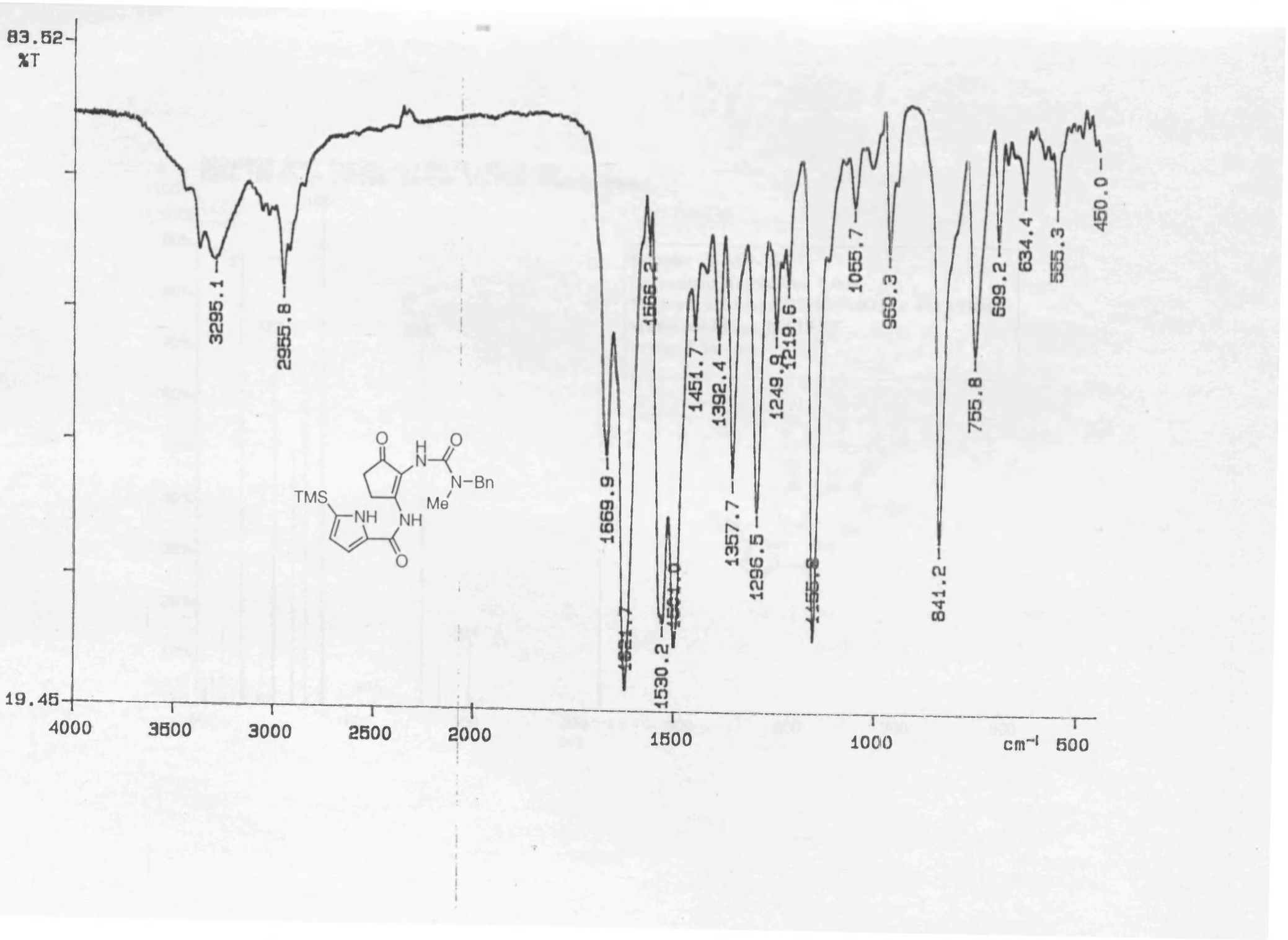


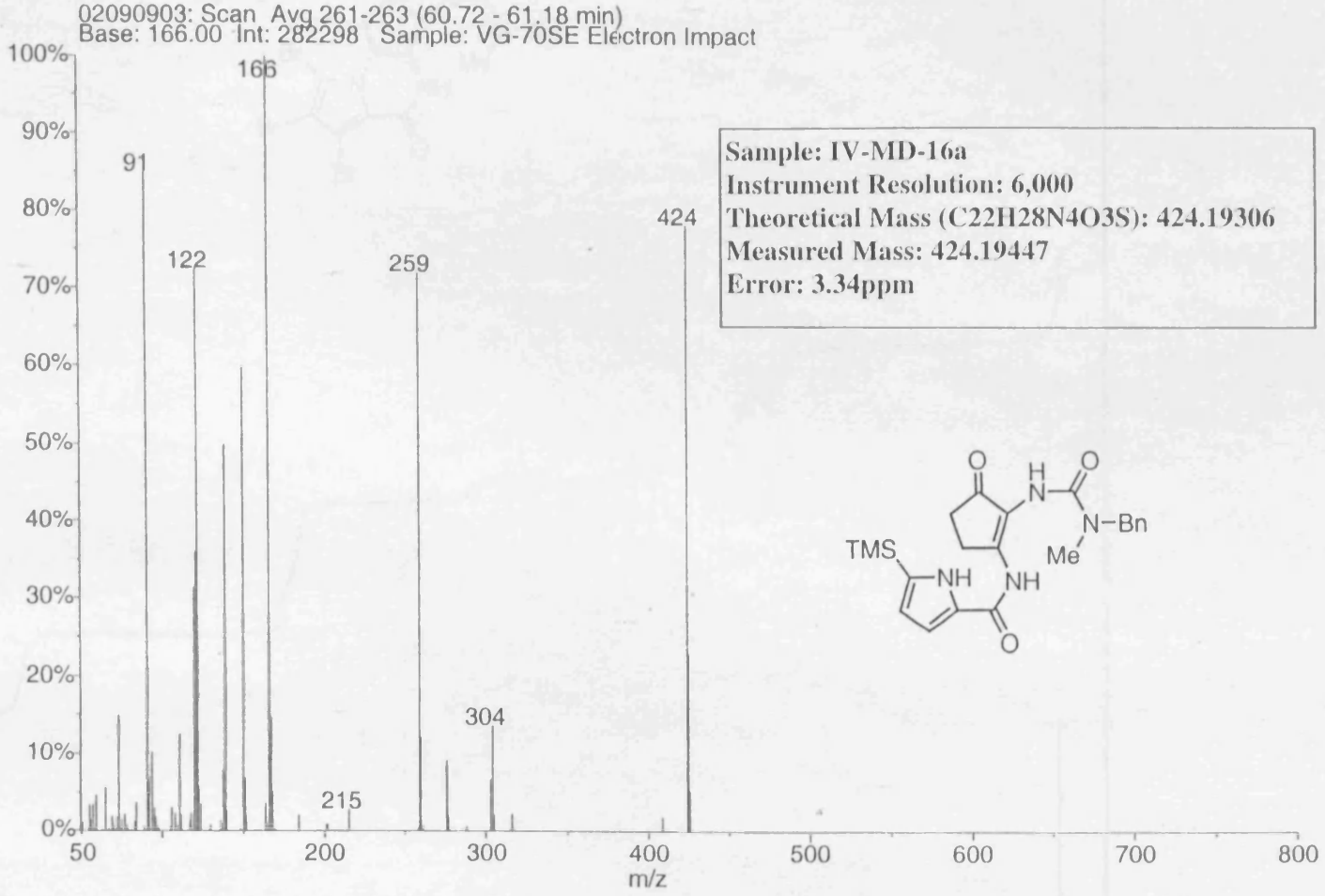


IV-md-16a
CDCl3, 298 K
HMQC

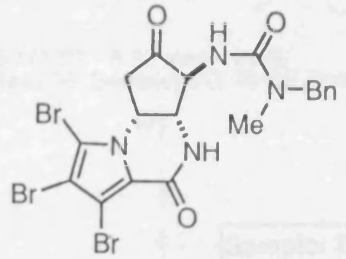


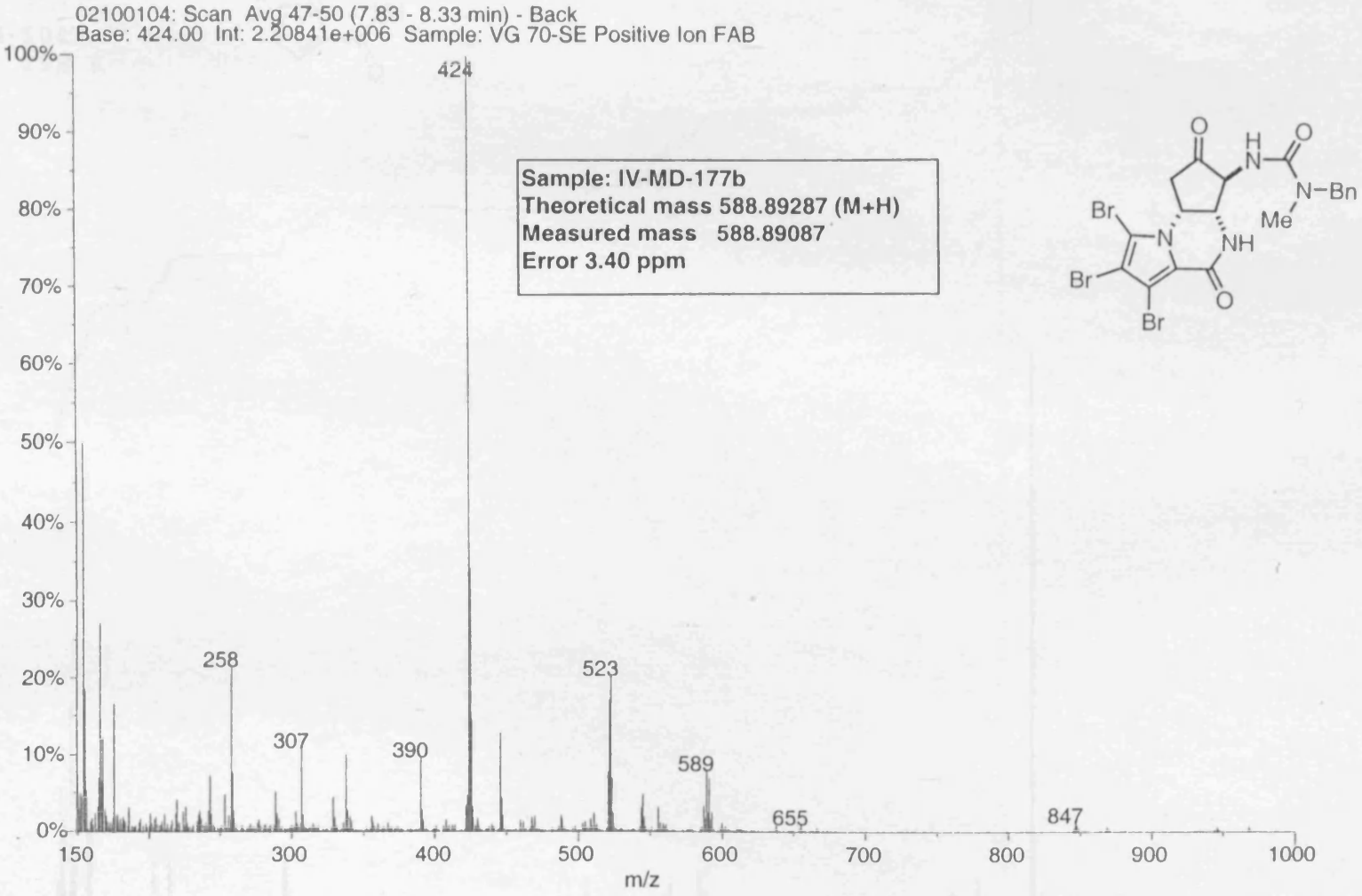


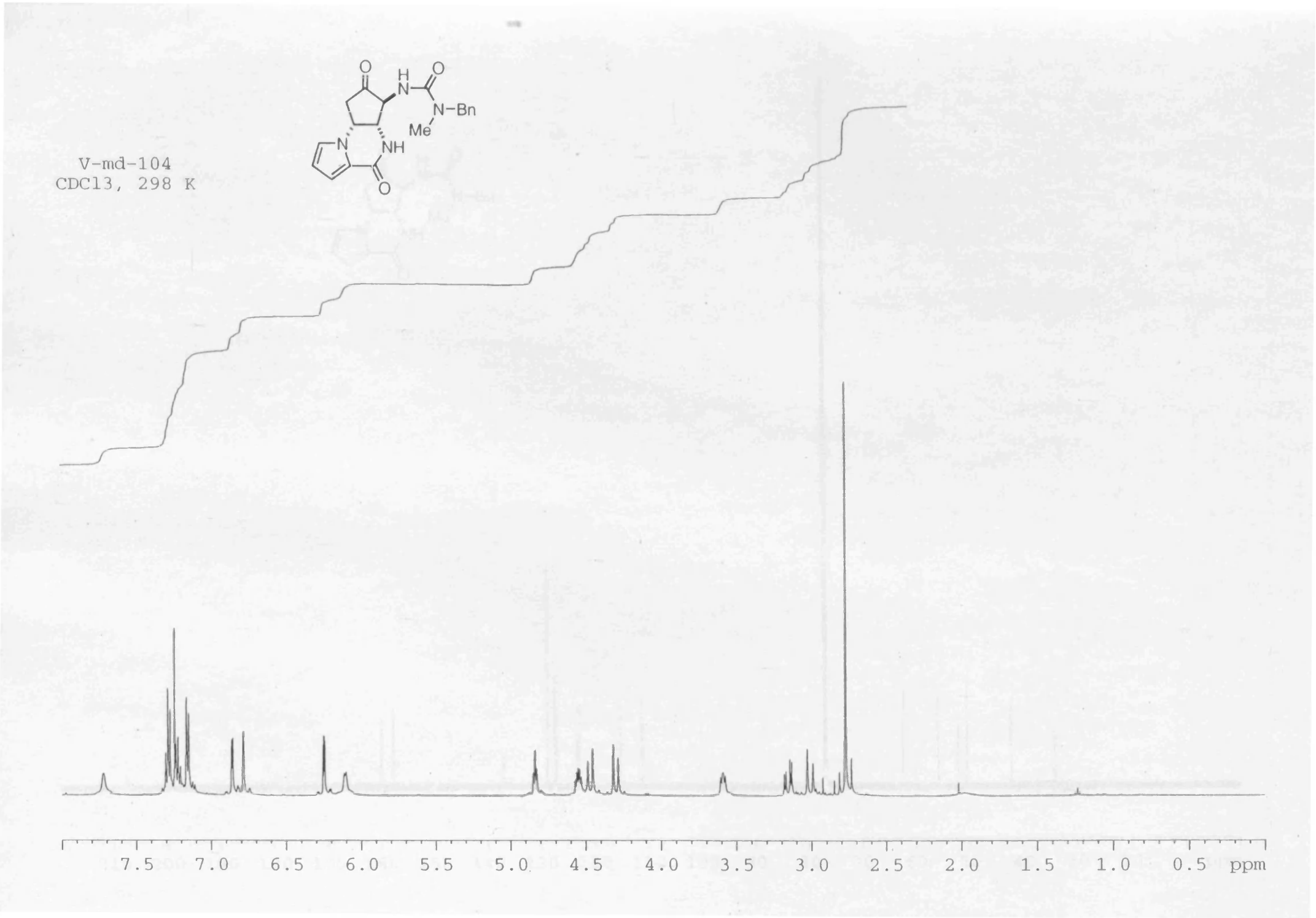

83.52
%T
19.45
3295.1
2955.8
1669.9
1566.2
1530.2
1451.7
1392.4
1357.7
1296.5
1249.9
1219.6
1055.7
969.3
841.2
755.8
699.2
634.4
555.3
450.0
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
500
TMS
NH
NH
N–Bn
Me
O


02090903: Scan Avg 261-263 (60.72 - 61.18 min)
Base: 166.00 Int: 282298 Sample: VG-70SE Electron Impact
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
166
91
122
259
424
304
215
50
200
300
400
500
600
700
800
m/z
Sample: IV-MD-16a
Instrument Resolution: 6,000
Theoretical Mass (C22H28N4O3S): 424.19306
Measured Mass: 424.19447
Error: 3.34ppm
TMS
NH
NH
N
H
O
O
O
N–Bn
Me

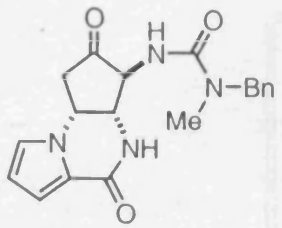
IV-md-177b
CDCl3, 298 K



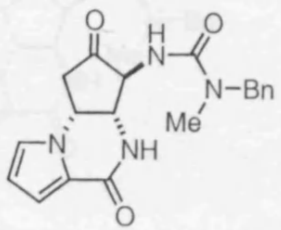

02100104: Scan Avg 47-50 (7.83 - 8.33 min) - Back
Base: 424.00 Int: 2.20841e+006 Sample: VG 70-SE Positive Ion FAB
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
424
258
307
390
523
589
655
847
150
300
400
500
600
700
800
900
1000
m/z
Sample: IV-MD-177b
Theoretical mass 588.89287 (M+H)
Measured mass 588.89087
Error 3.40 ppm
O
H
N
O
N–Bn
Me
Br
N
NH
Br
O
Br

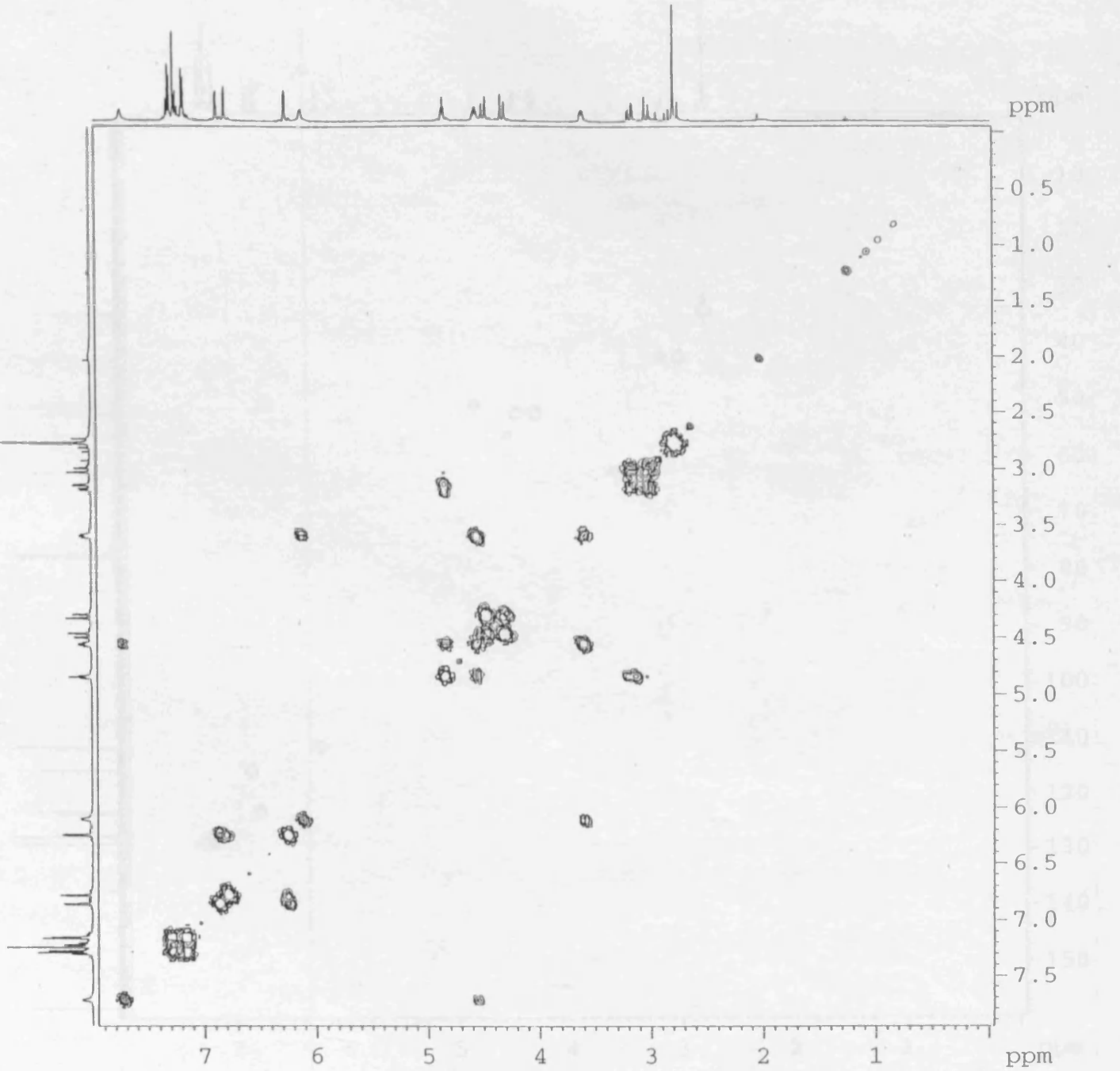

V-md-104
CDCl3, 298 K
O
H
N
O
N–Bn
Me
N
NH
O
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

V-md-104
CDCl3, 298 K

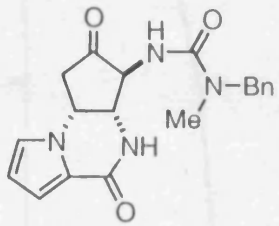


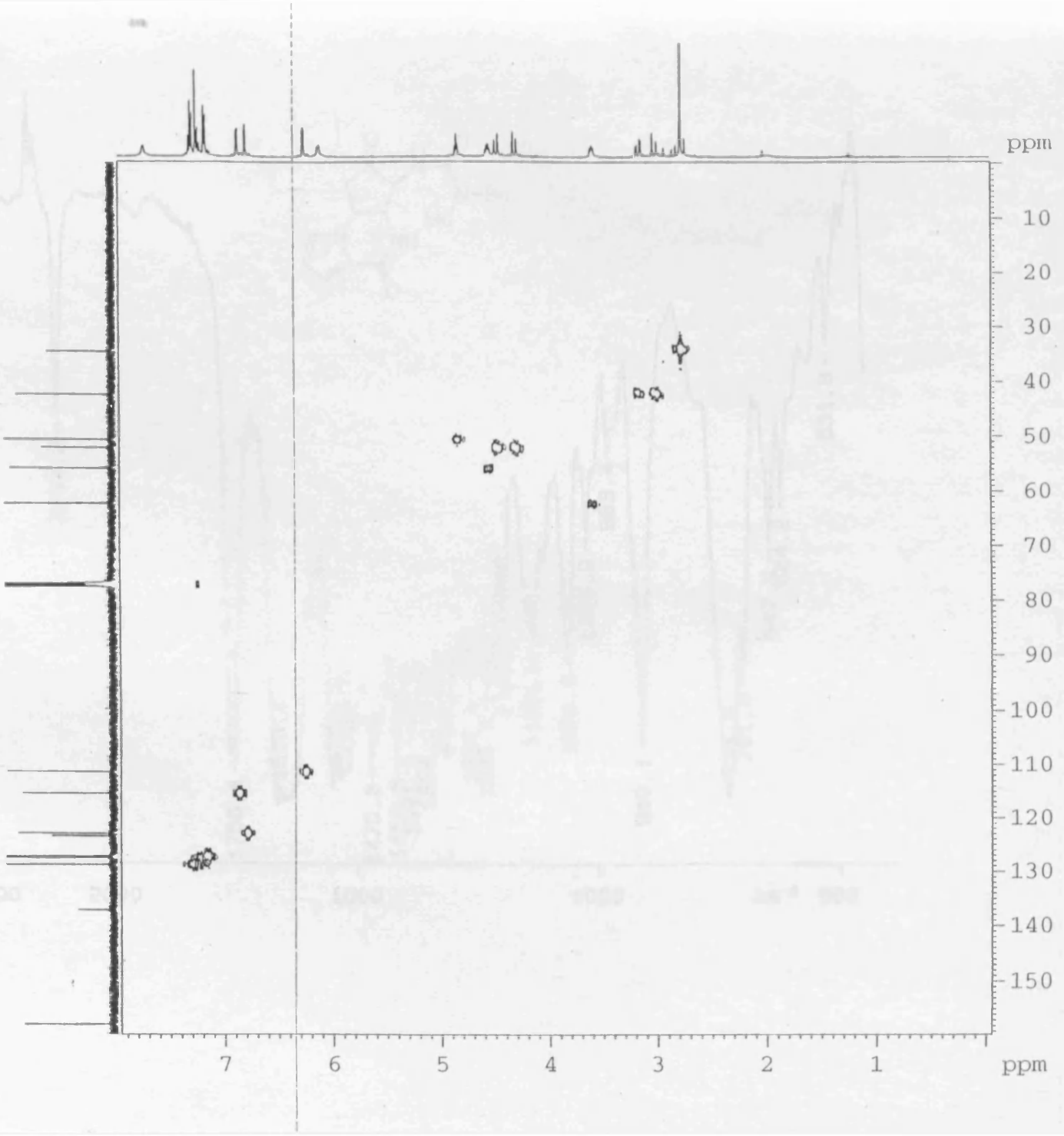
V-md-104
CDC13, 298 K
COSY

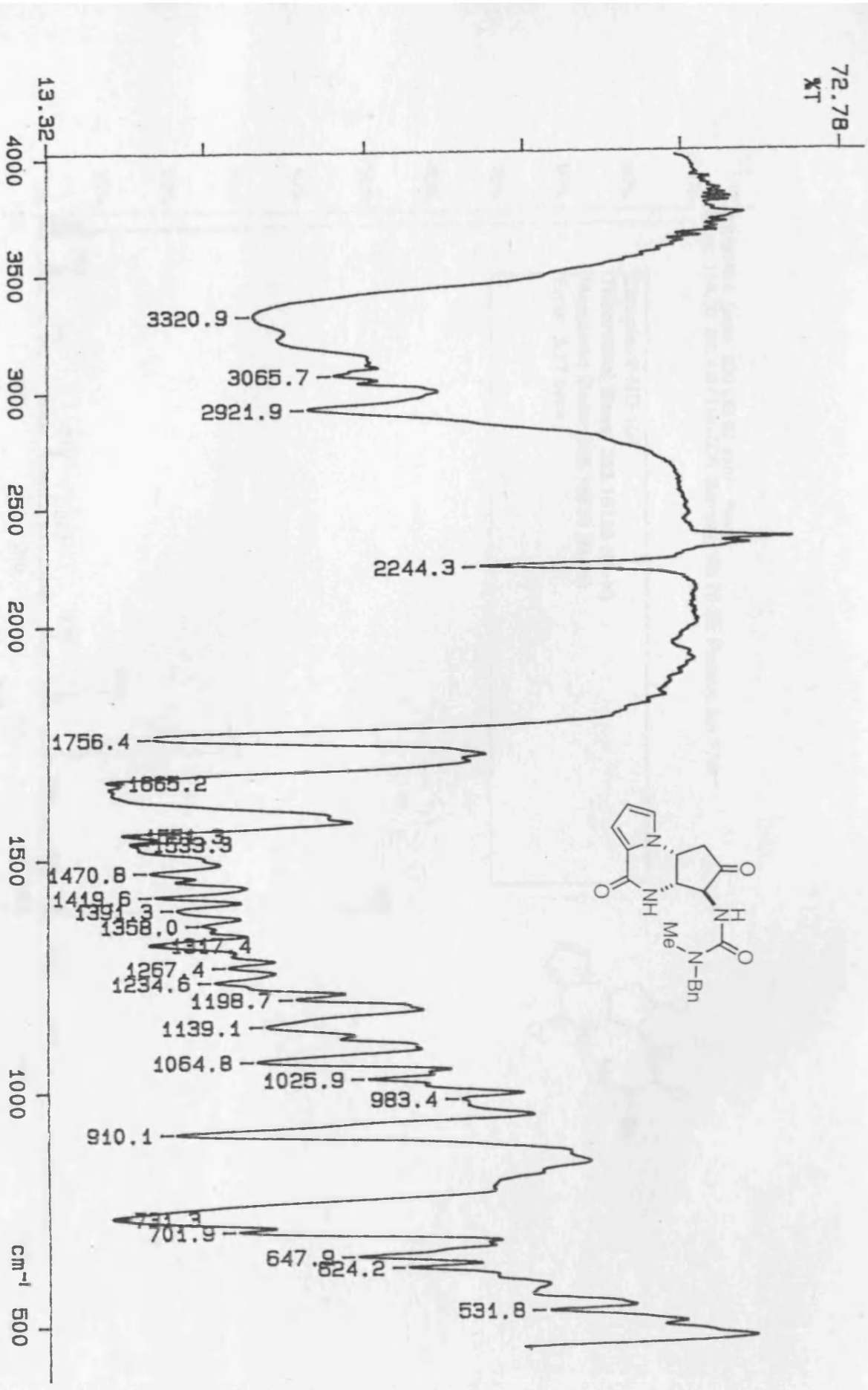


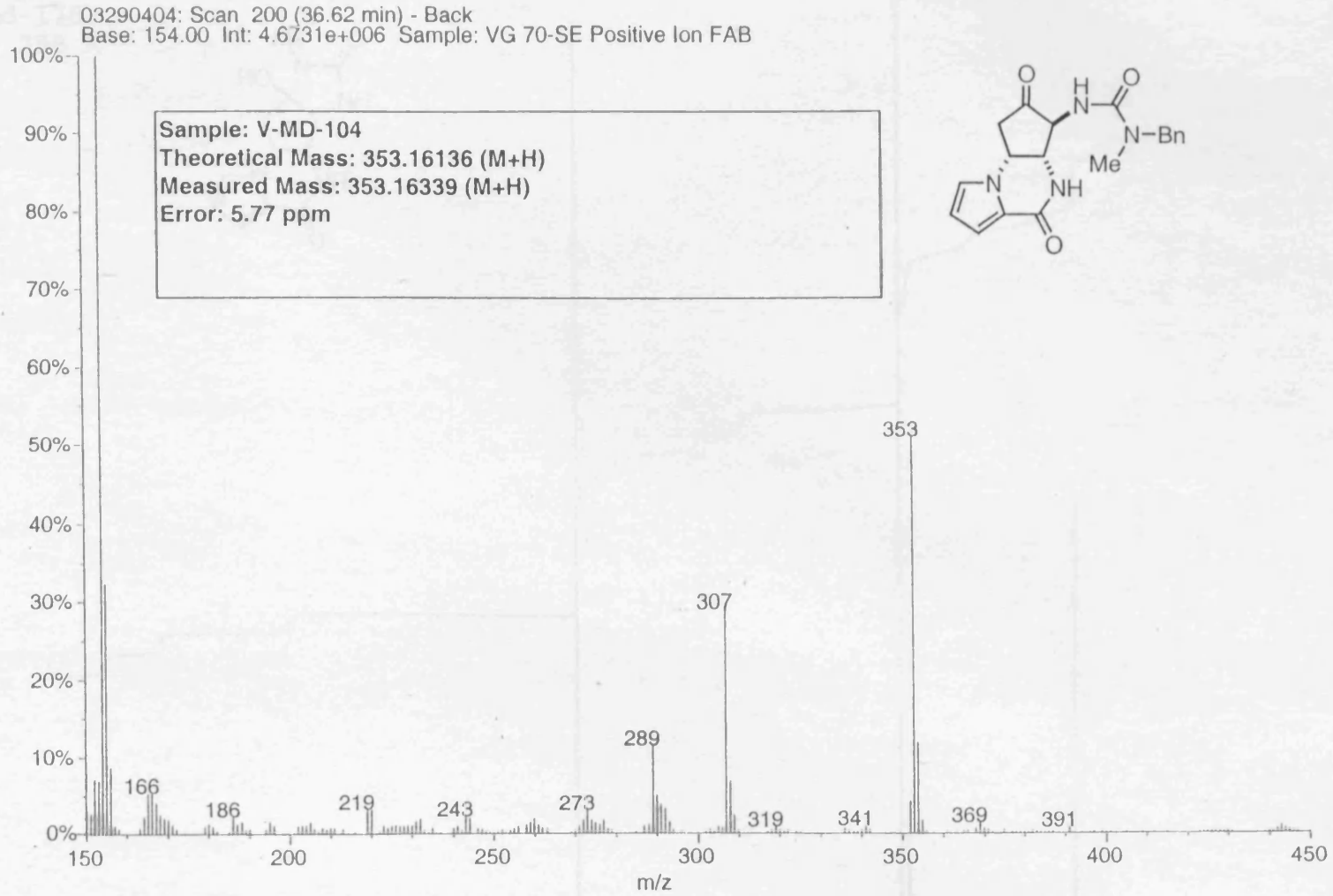


V-md-104
CDCl3, 298 K
HMQC

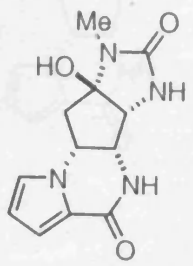




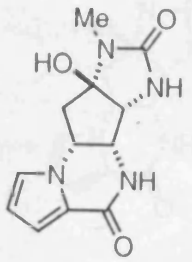

72.78
%T
13.32
4000
3500
3000
2500
2000
1500
1000
500
cm-1
3320.9
3065.7
2921.9
2244.3
1756.4
1665.2
1470.8
1419.6
1391.3
1358.0
1267.4
1234.6
1198.7
1139.1
1064.8
1025.9
983.4
910.1
701.9
647.8
624.2
531.8
O
N
H
N
O
O
N
H
Me
N-Bn

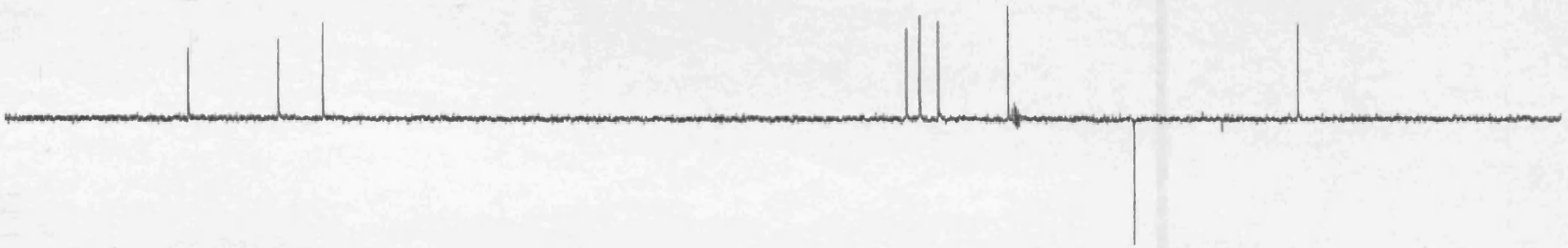

03290404: Scan 200 (36.62 min) - Back
Base: 154.00 Int: 4.6731e+006 Sample: VG 70-SE Positive Ion FAB
Sample: V-MD-104
Theoretical Mass: 353.16136 (M+H)
Measured Mass: 353.16339 (M+H)
Error: 5.77 ppm
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
150
200
250
300
350
400
450
m/z
353
307
289
166
186
219
243
273
319
341
369
391
O
H
N
O
N–Bn
Me
N
NH
O

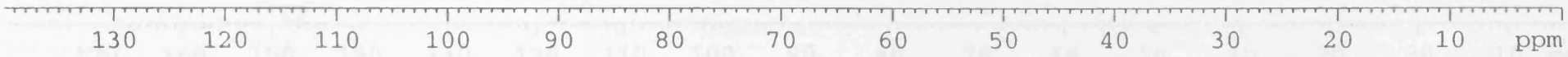
IV-md-178
MeOD, 298 K

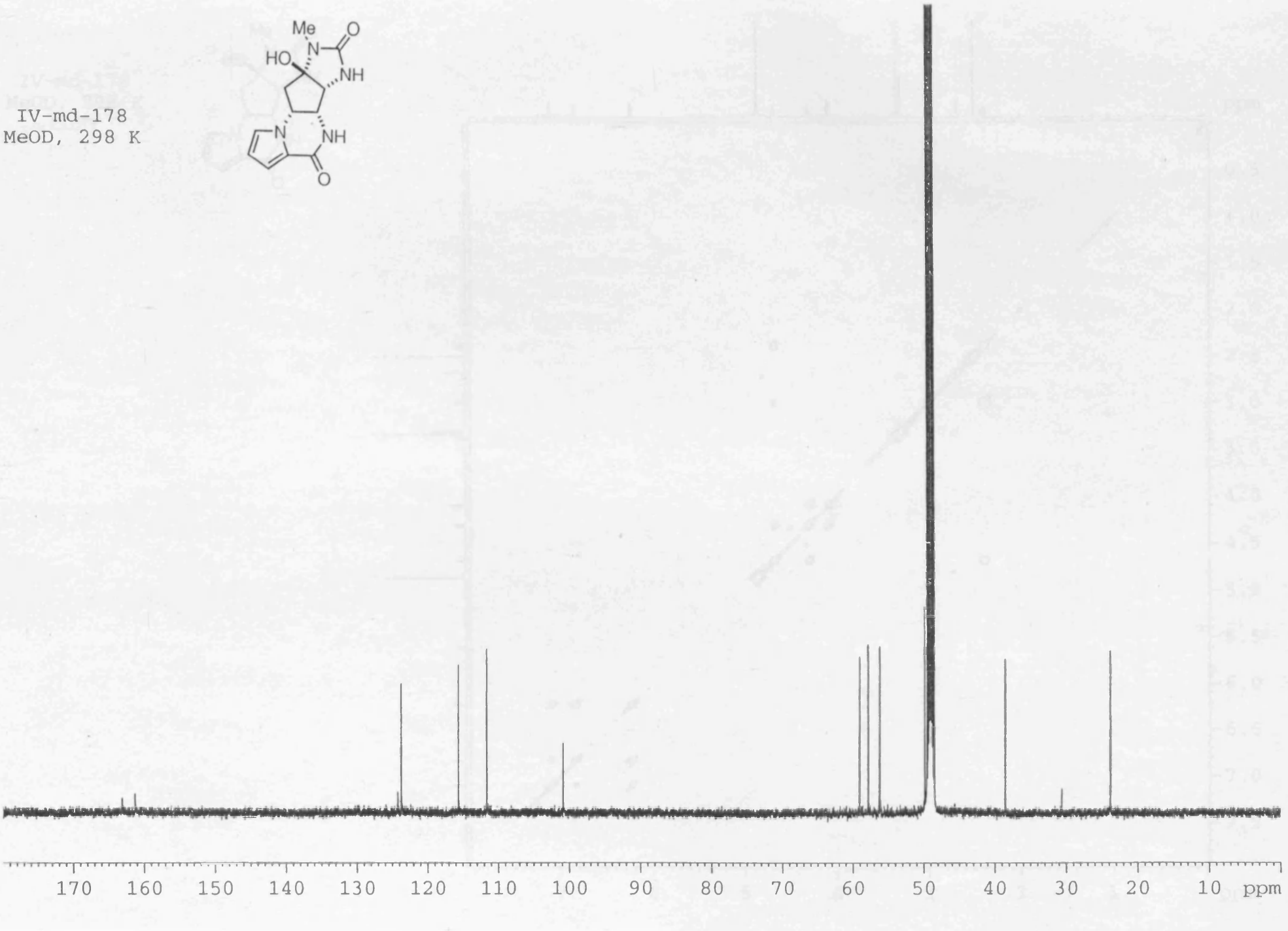


IV-md-178
MeOD, 298 K
DEPT

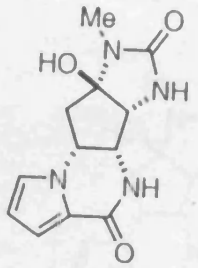


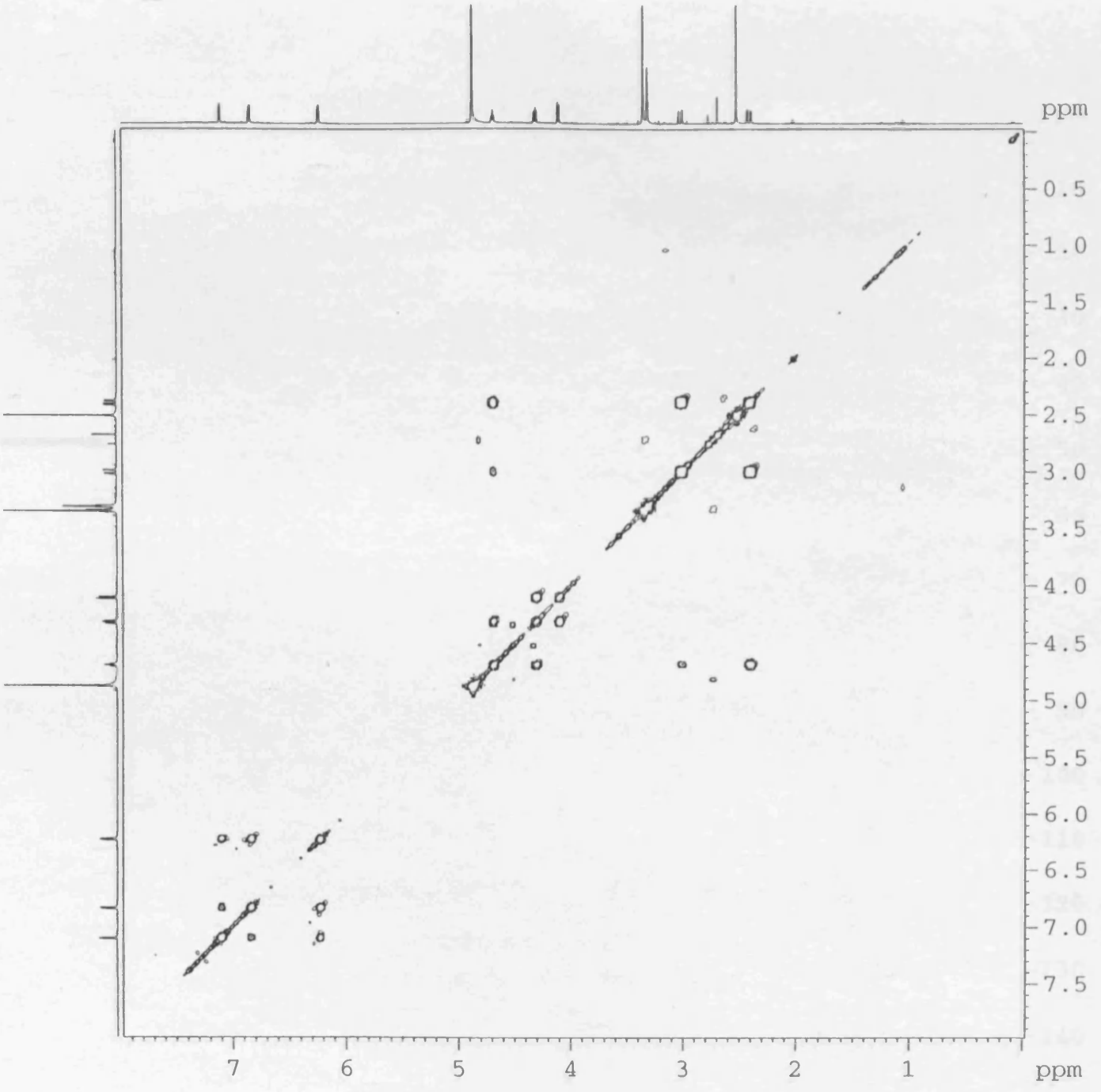




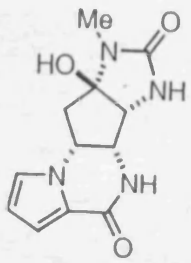

IV-md-178
MeOD, 298 K
Me
N
O
HO
NH
N
NH
O
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

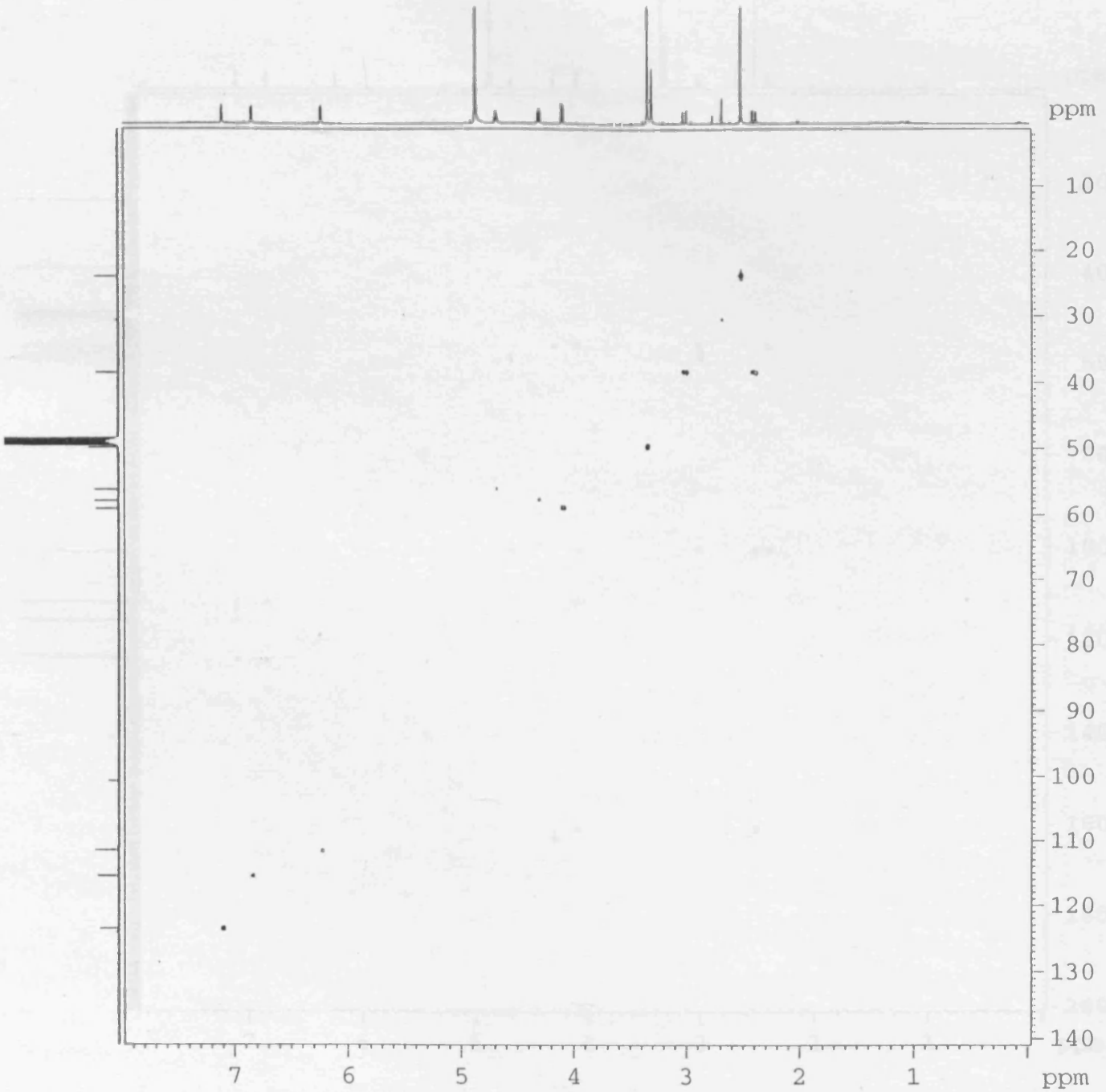
IV-md-178
MeOD, 298 K
COSY



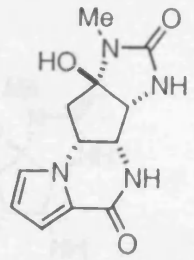


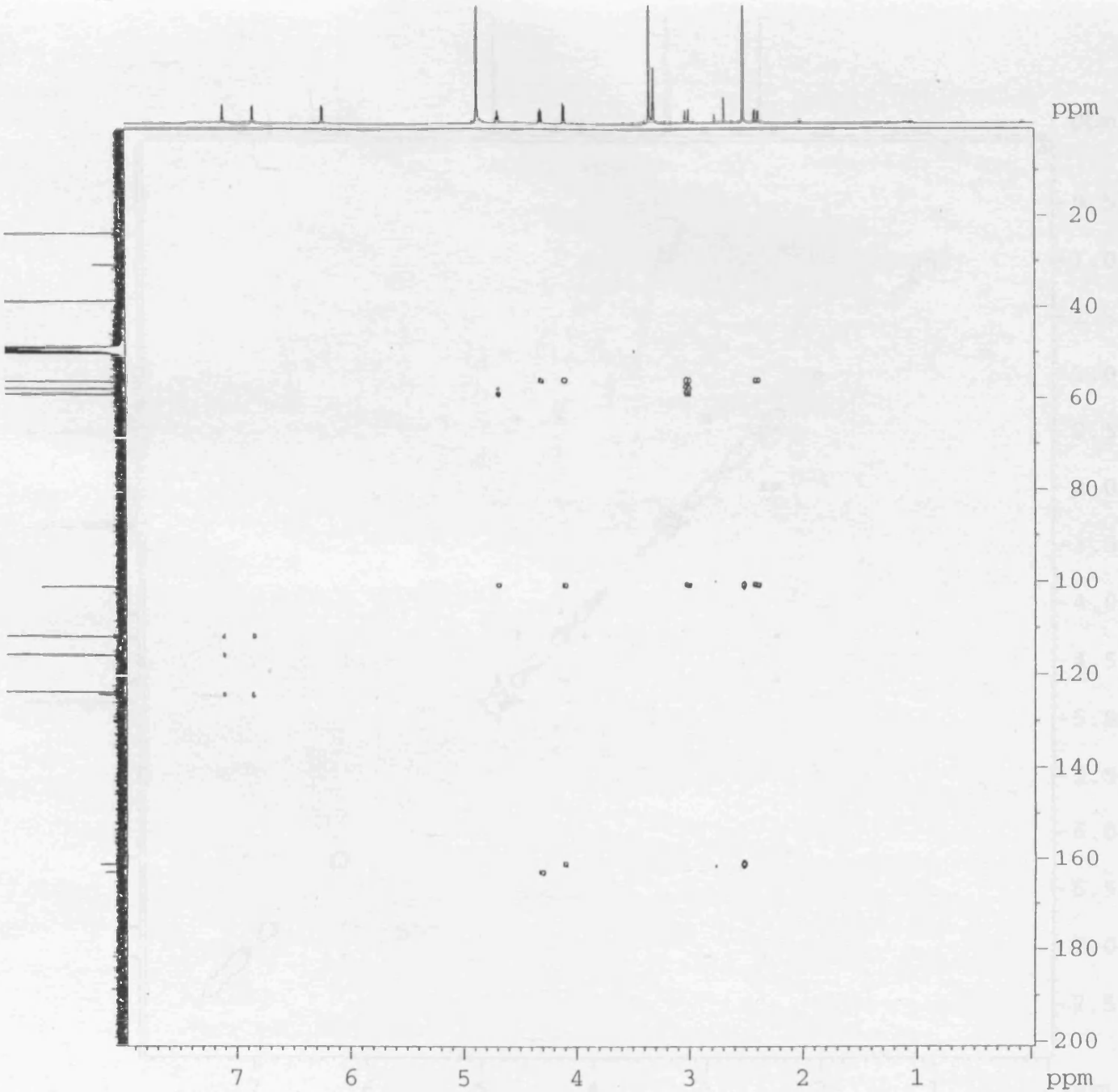
IV-md-178
MeOD, 298 K
HMQC



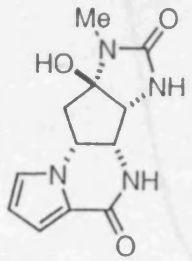


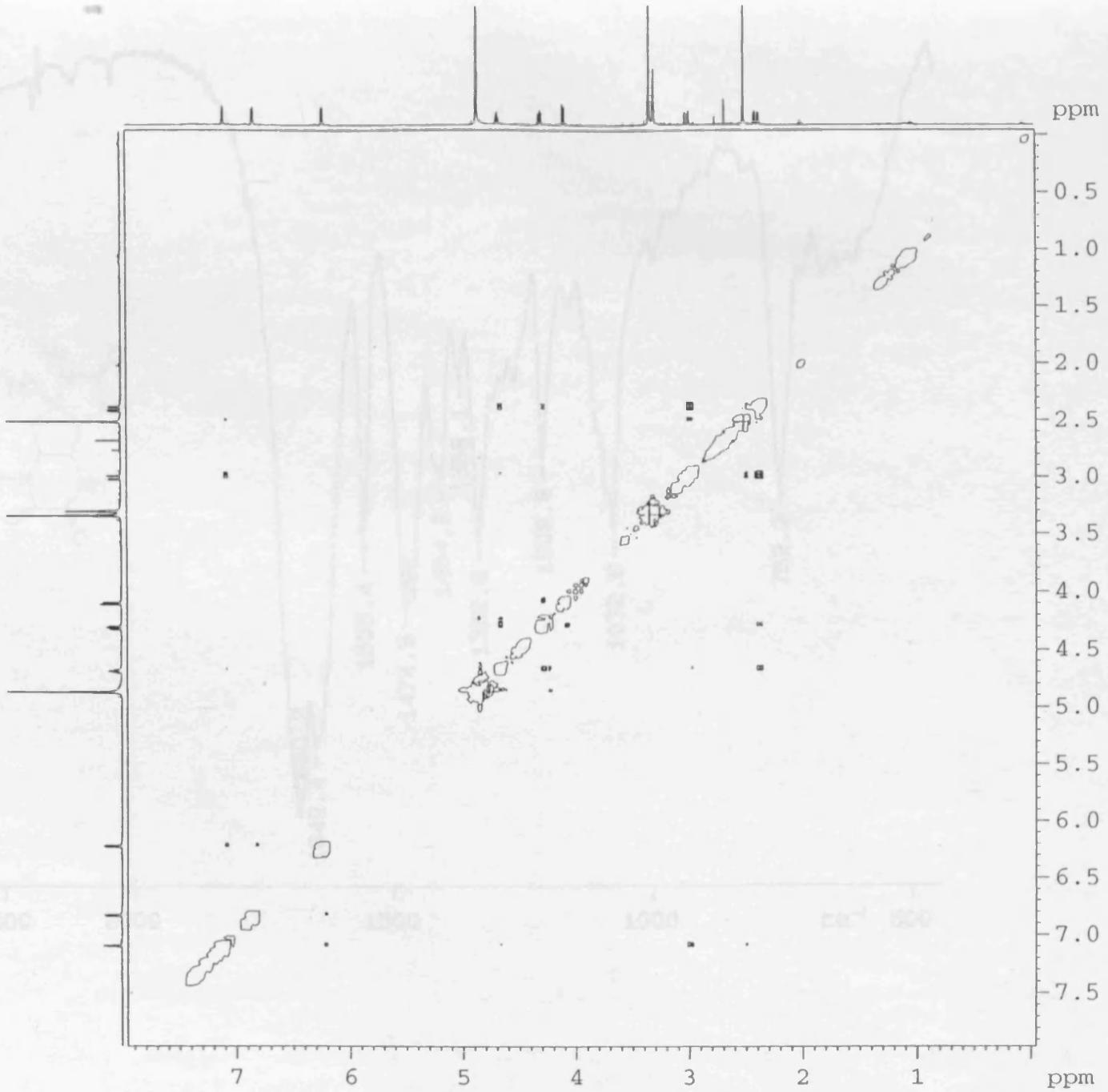
IV-md-178
MeOD, 298 K
HMBC

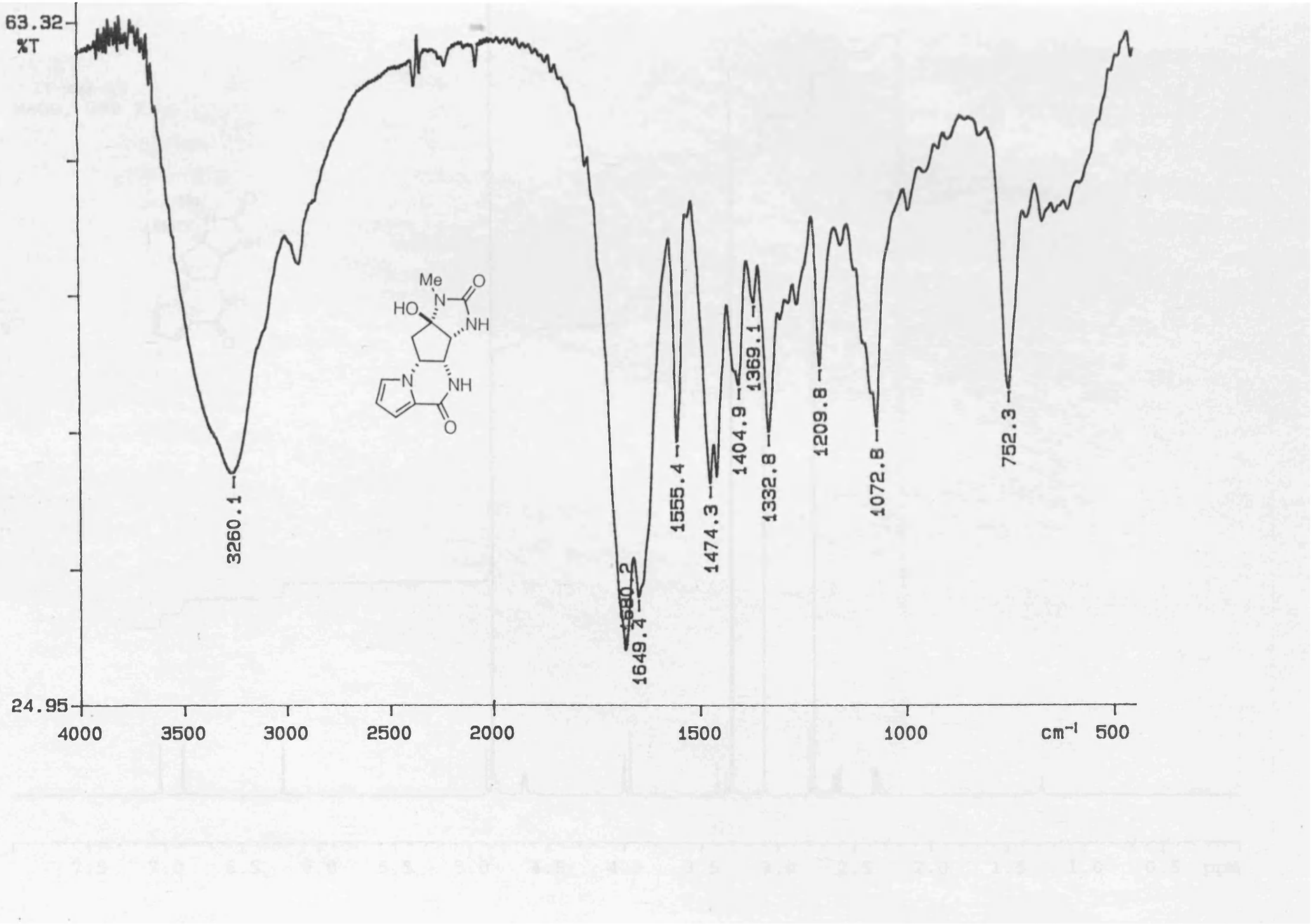




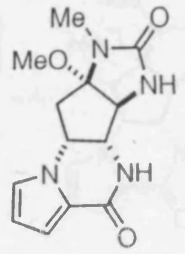
IV-md-178
MeOD, 298 K
NOESY



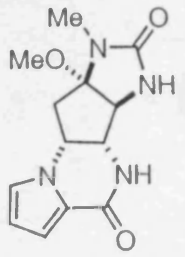


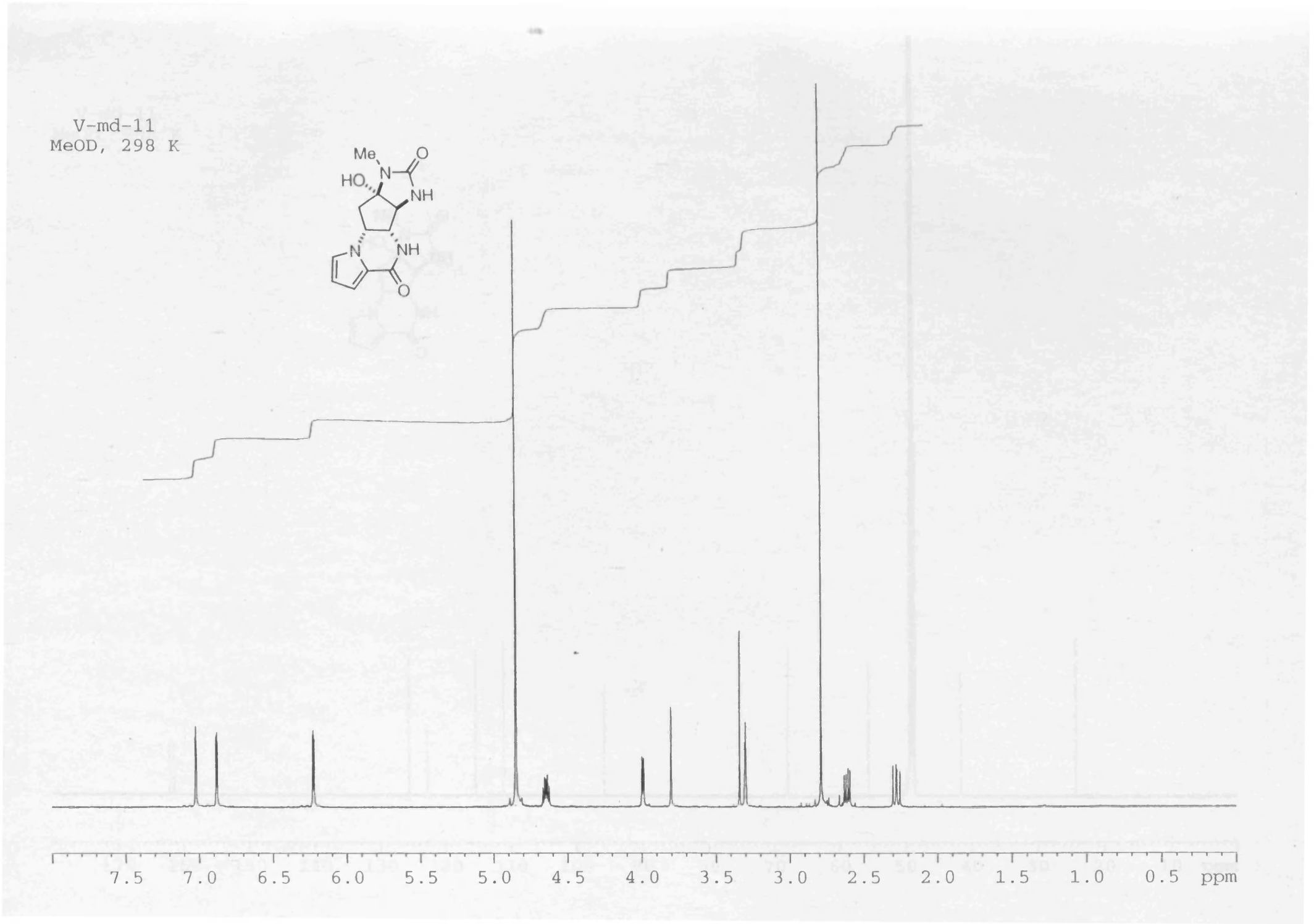

63.32
%T
24.95
3260.1
1649.4
1555.4
1474.3
1404.9
1369.1
1332.8
1209.8
1072.8
752.3
4000
3500
3000
2500
2000
1500
1000
cm-1
500
Me
N
O
HO
NH
N
NH
O

IV-md-58
MeOD, 298 K

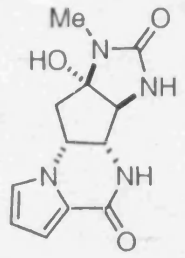


IV-md-58
MeOD, 298 K

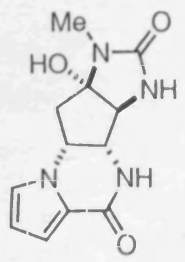


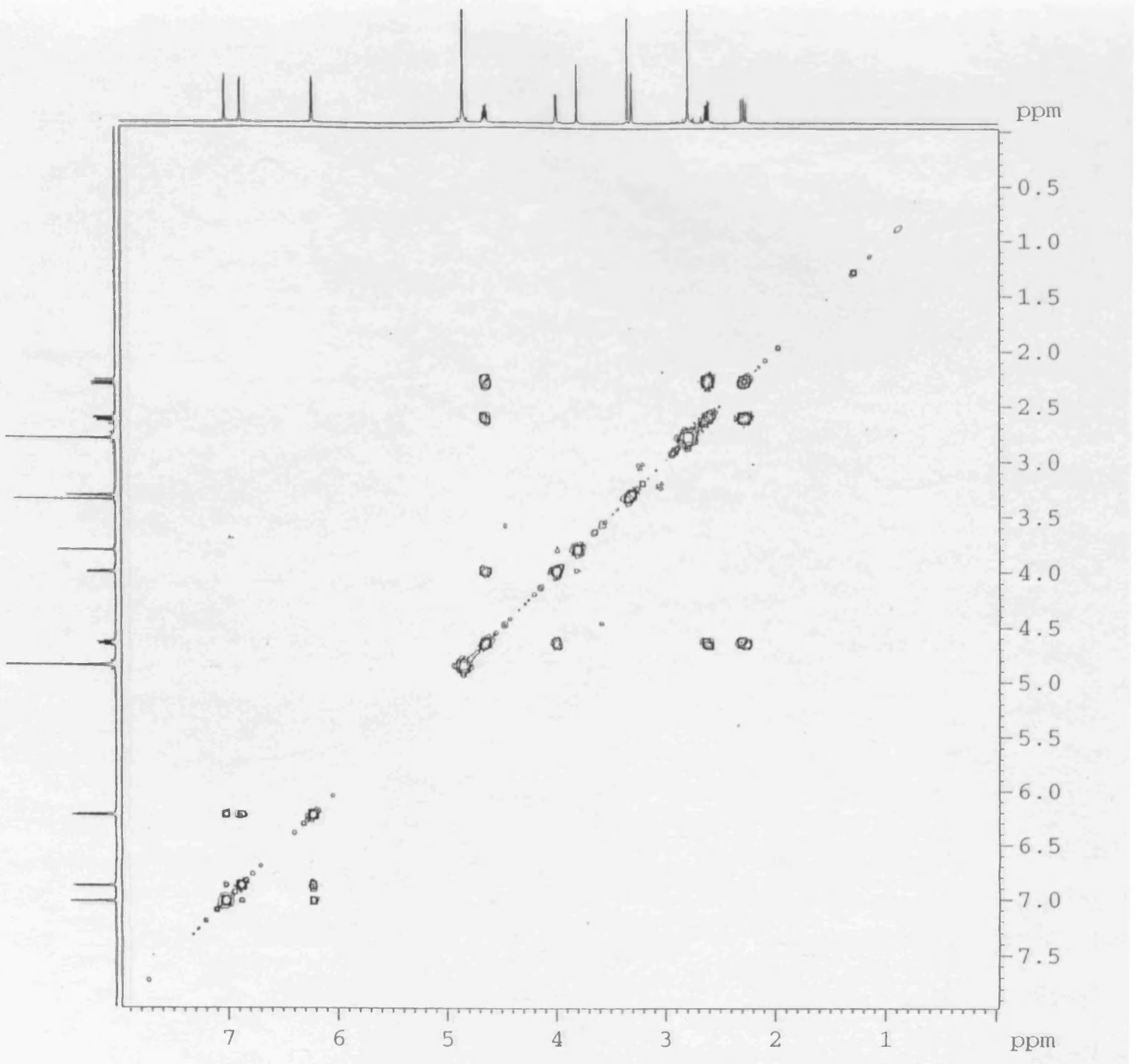

V-md-11
MeOD, 298 K
Me
N
O
HO
NH
N
NH
O
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

V-md-11
MeOD, 298 K

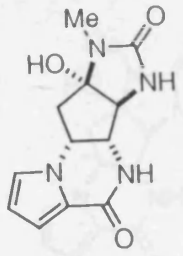


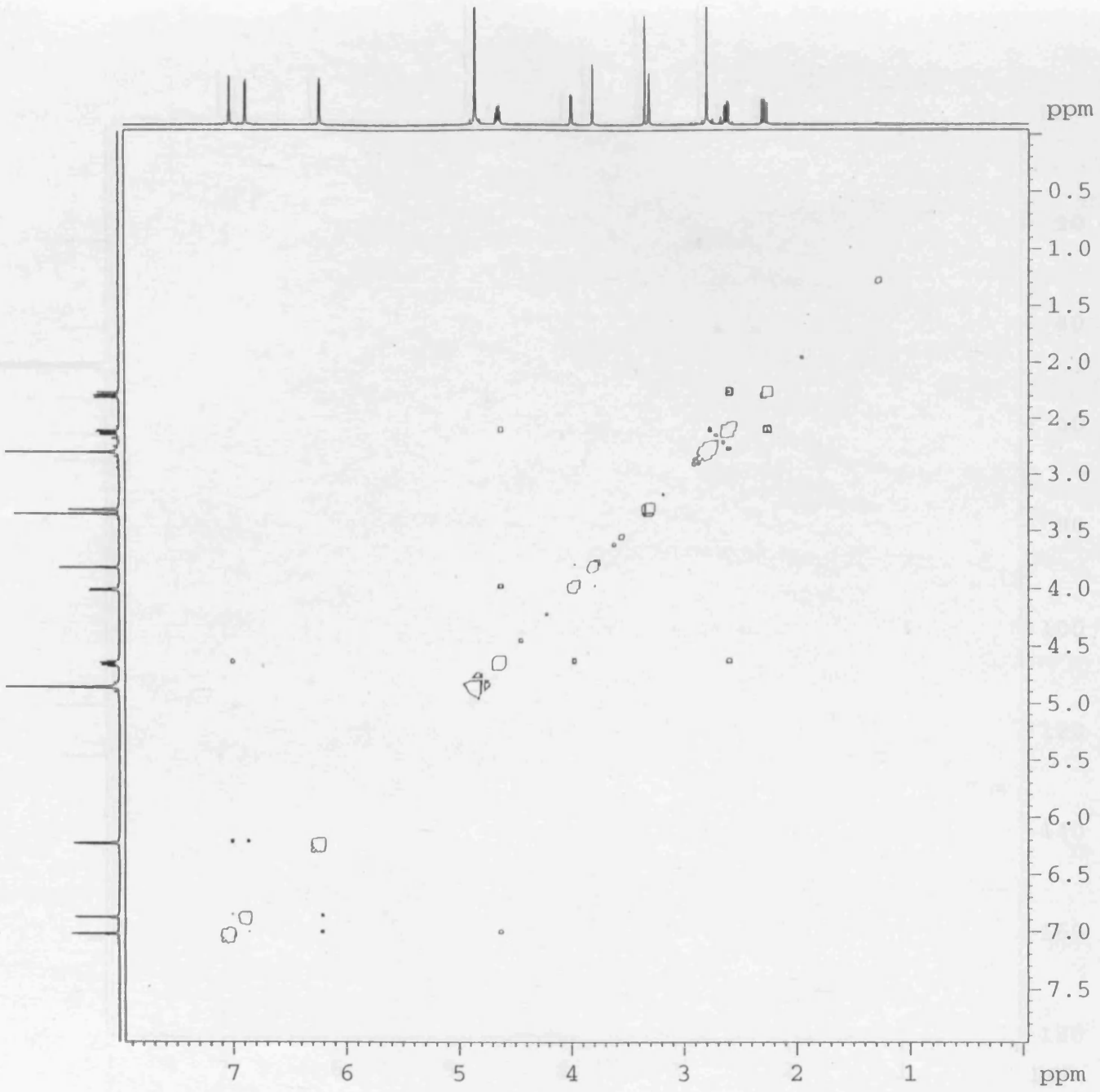
V-md-11
MeOD, 298 K
COSY



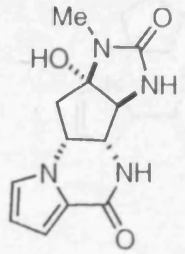


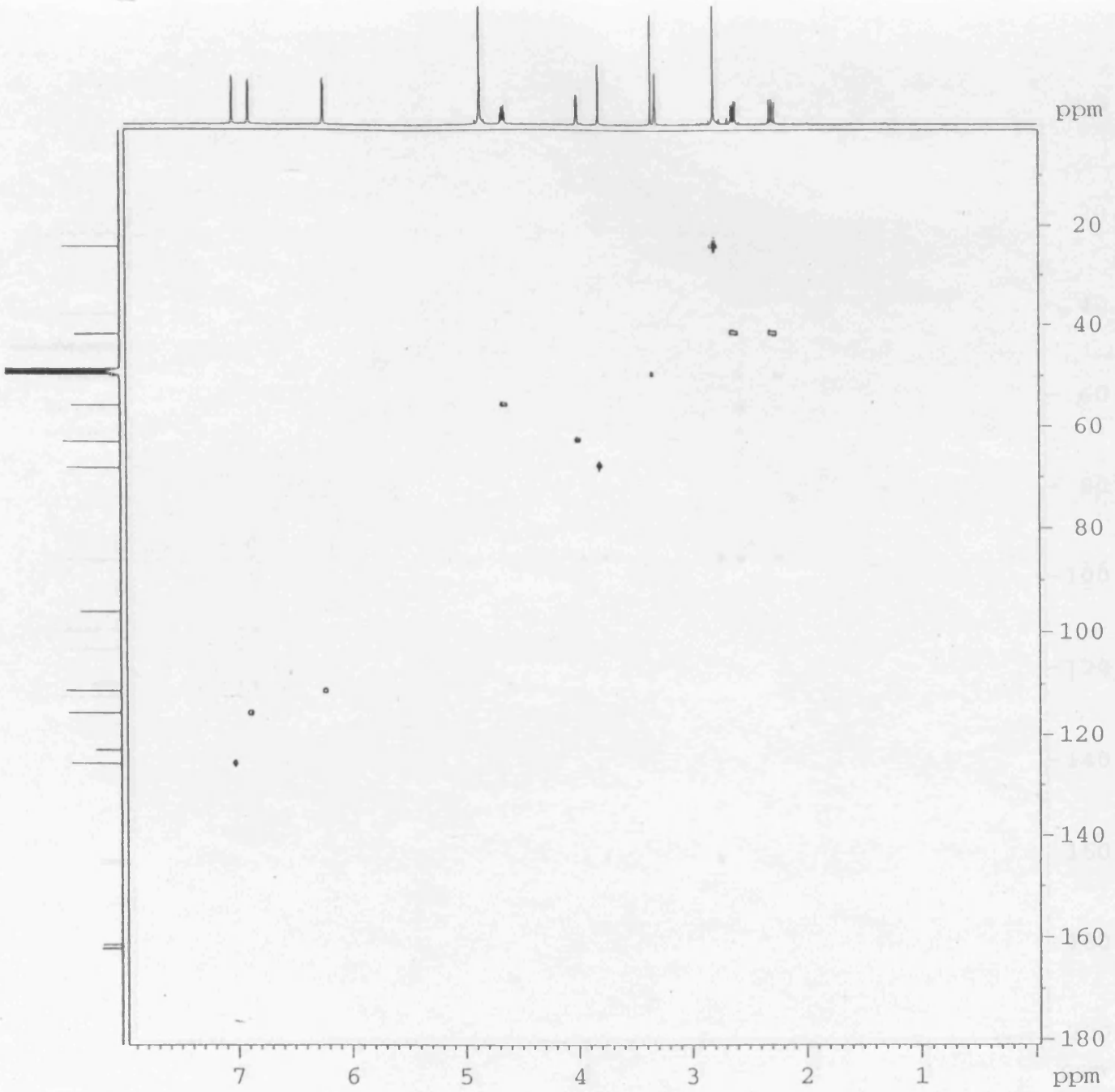
V-md-11
MeOD, 298 K
NOESY



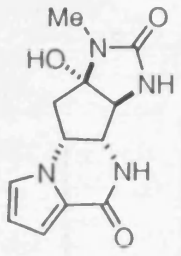


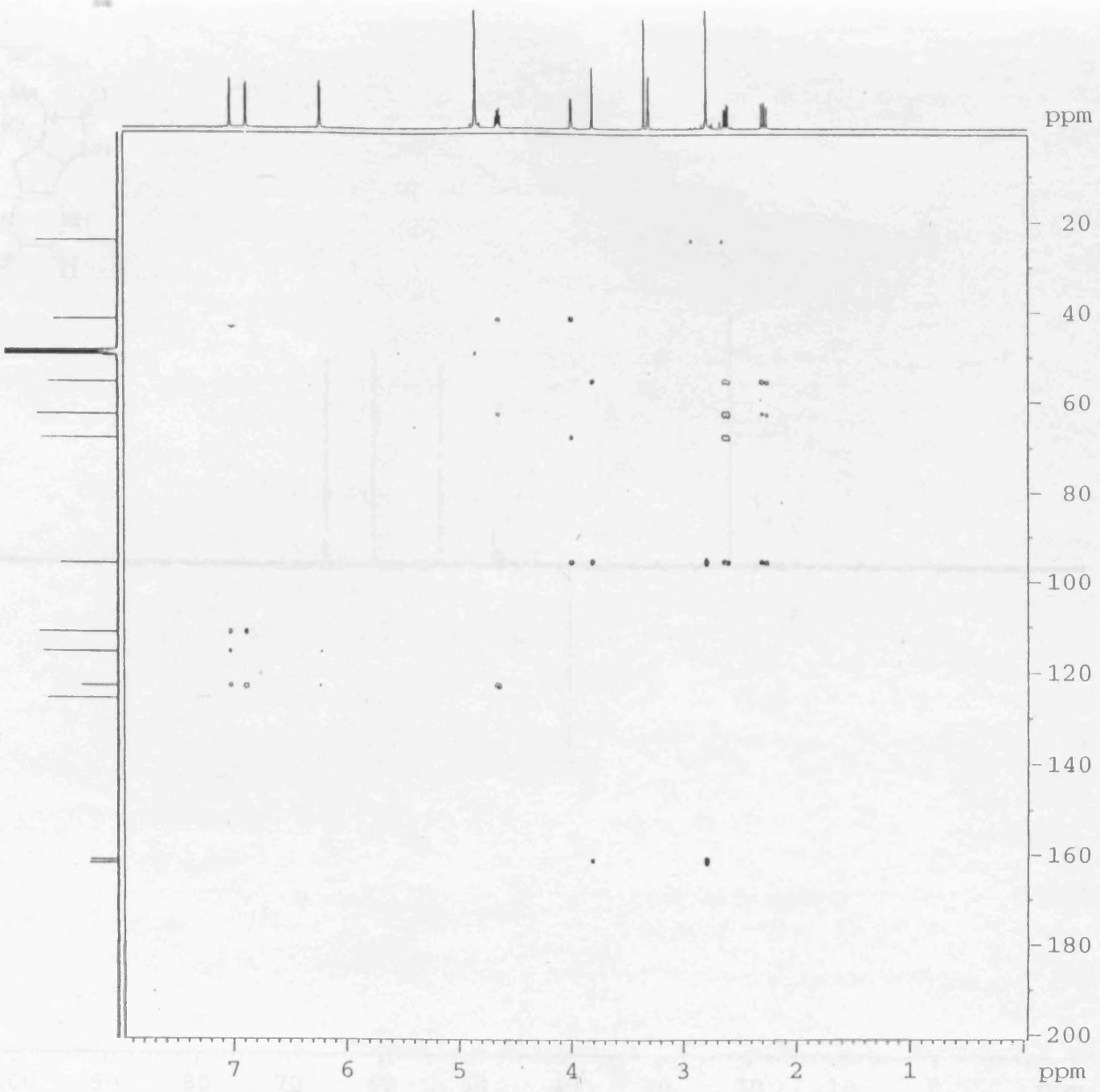
V-md-11
MeOD, 298 K
HMQC



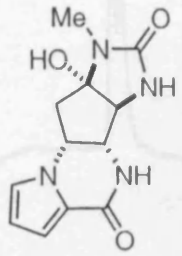


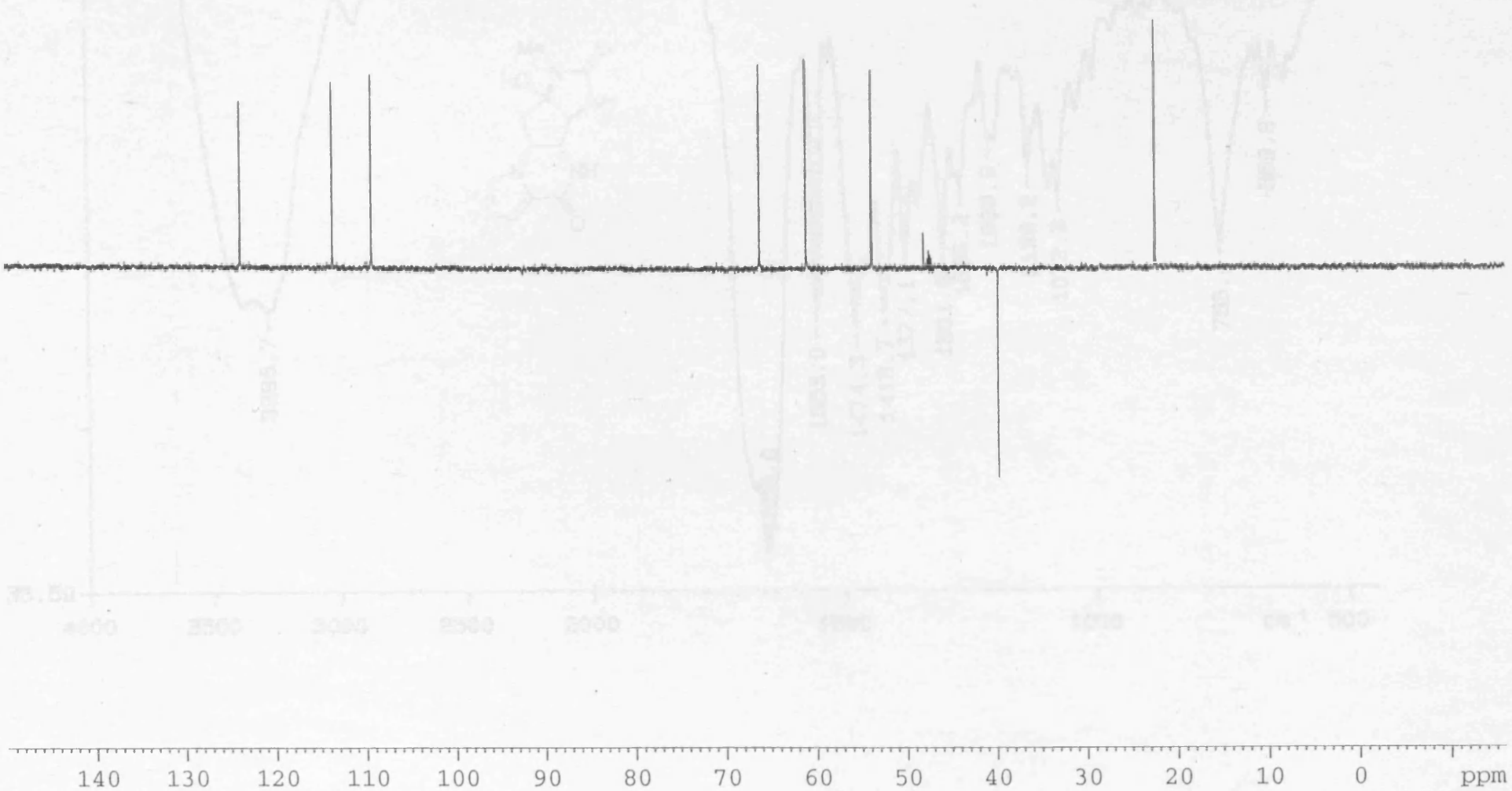
V-md-11
MeOD, 298 K
HMBC

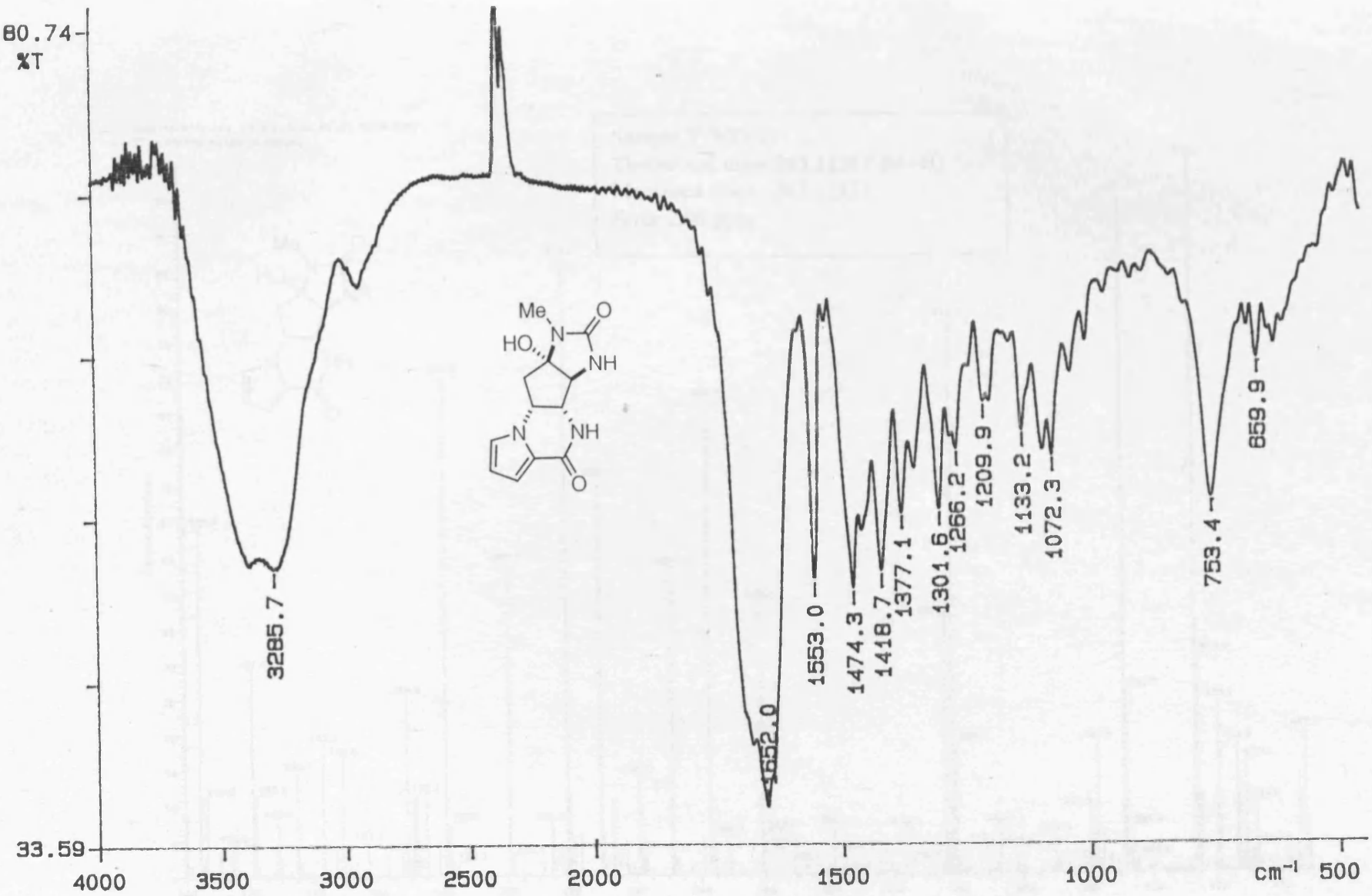


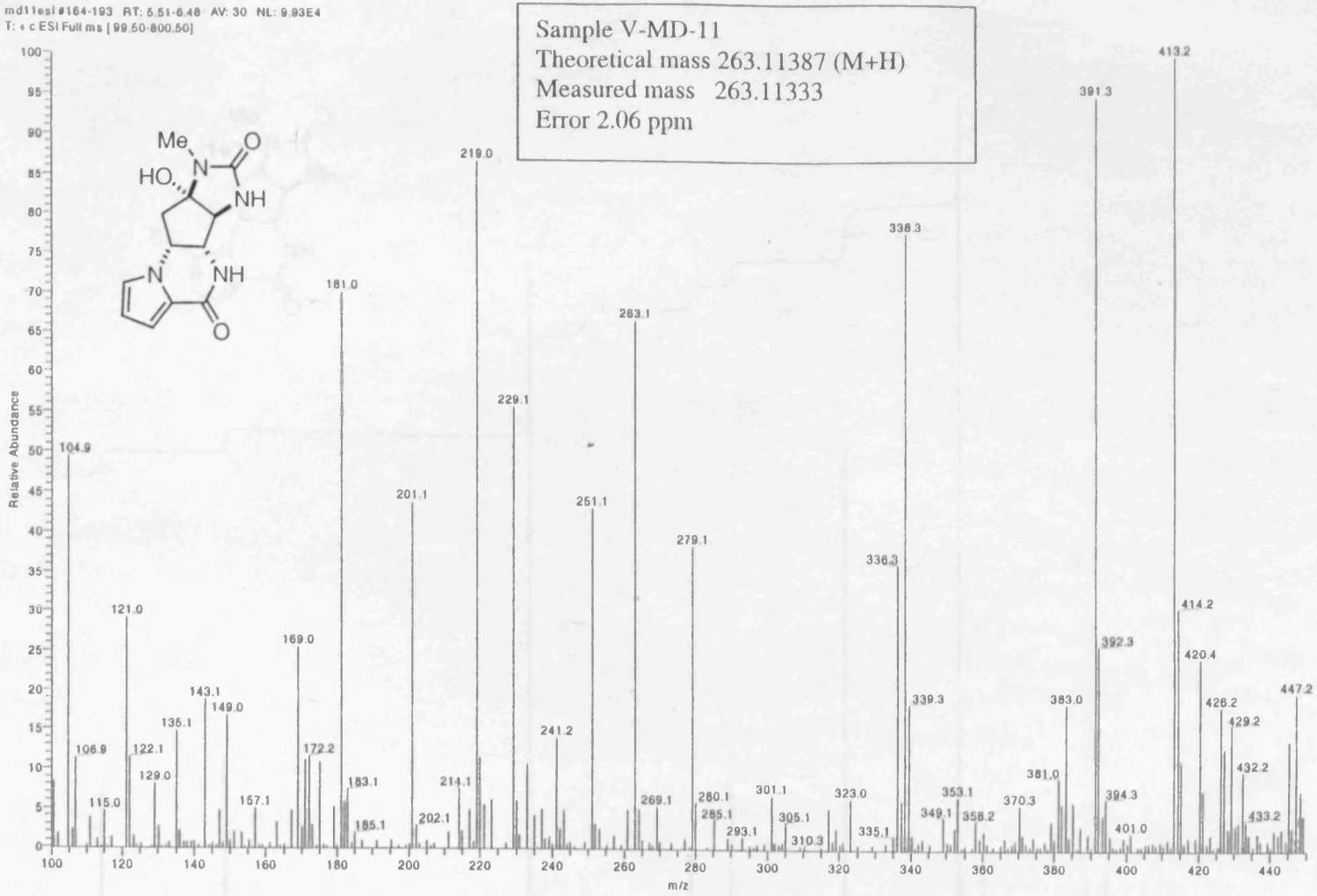


V-md-11
MeOD, 298 K
DEPT

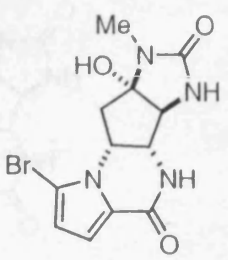




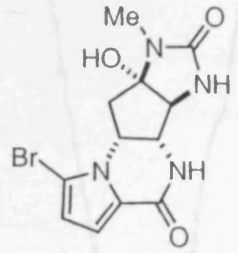

80.74
%T
33.59
4000
3500
3000
2500
2000
1500
1000
500
cm⁻¹
3285.7
1652.0
1553.0
1474.3
1418.7
1377.1
1301.6
1266.2
1209.9
1133.2
1072.3
753.4
859.9
Me
N
O
HO
NH
N
NH
O

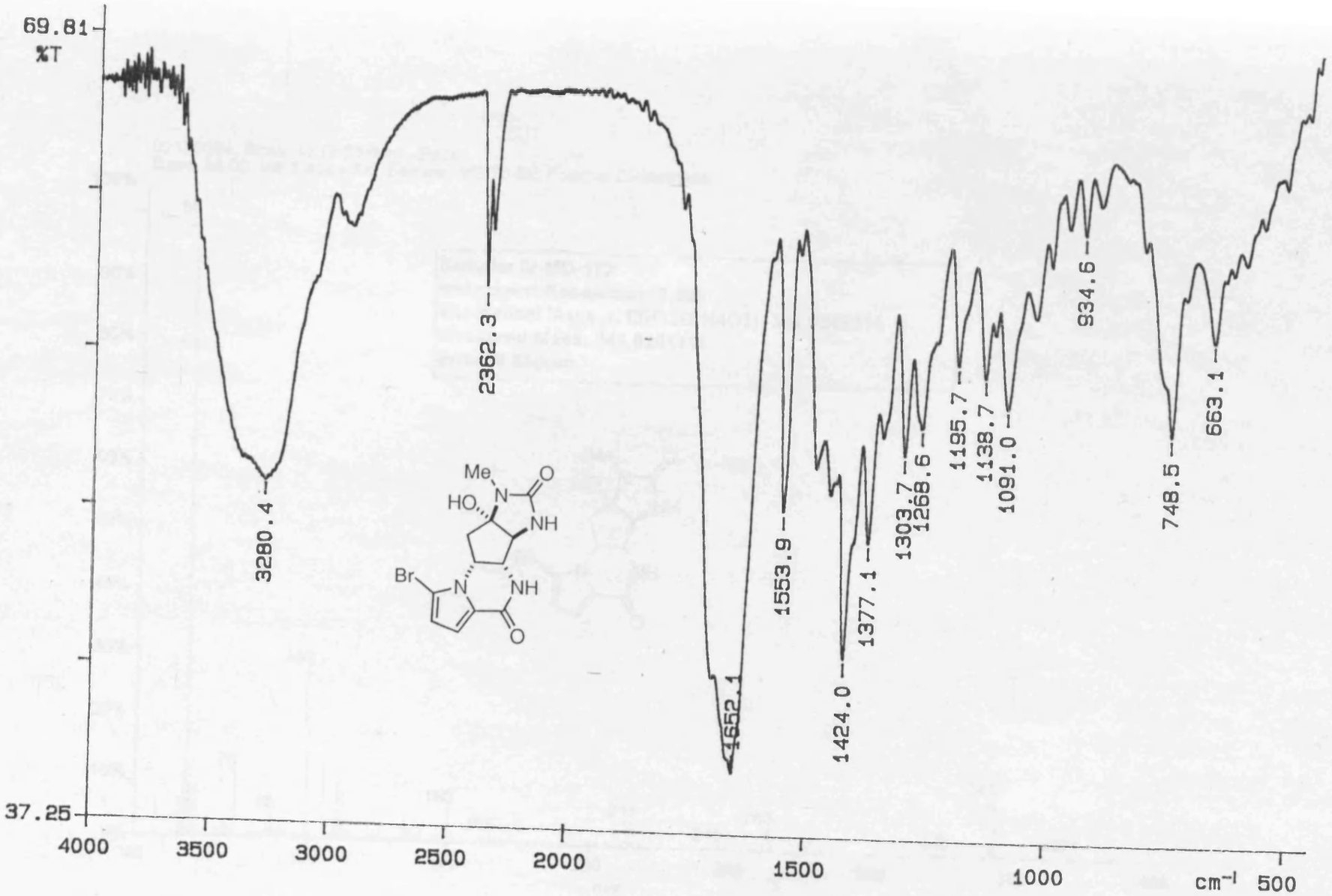

md11esi #164-193 RT: 5.51-6.48 AV: 30 NL: 9.93E4
T: + c ESI Full ms [99.50-800.50]
Sample V-MD-11
Theoretical mass 263.11387 (M+H)
Measured mass 263.11333
Error 2.06 ppm
Me
HO
N
O
NH
NH
N
O
Relative Abundance
m/z
104.9
106.9
115.0
121.0
122.1
129.0
135.1
143.1
149.0
157.1
169.0
172.2
181.0
183.1
185.1
201.1
202.1
214.1
219.0
229.1
241.2
251.1
263.1
269.1
279.1
280.1
285.1
293.1
301.1
305.1
310.3
323.0
335.1
336.3
338.3
339.3
349.1
353.1
358.2
370.3
381.0
383.0
391.3
392.3
394.3
401.0
413.2
414.2
420.4
426.2
429.2
432.2
433.2
447.2

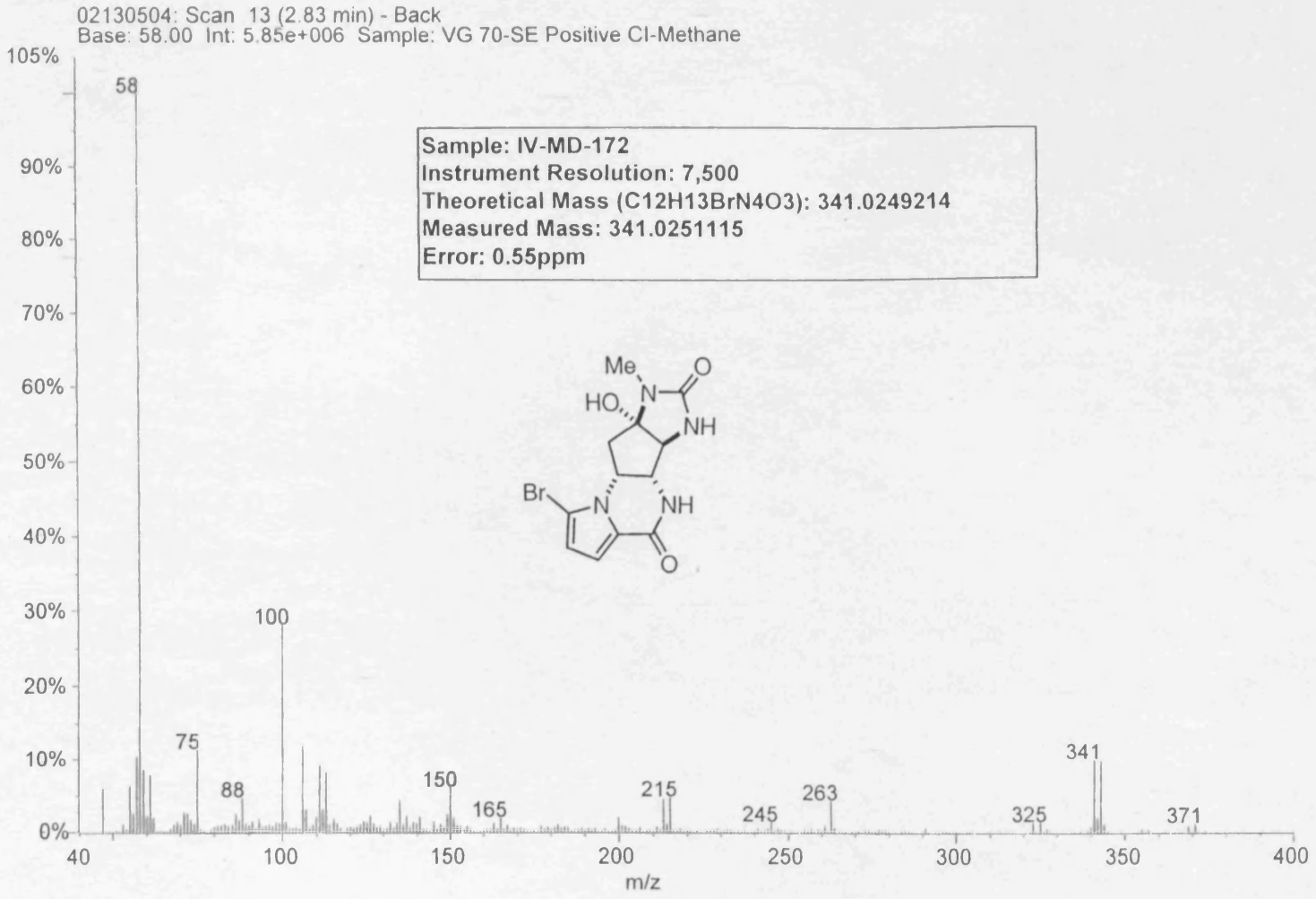
IV-md-172
MeOD, 298 K



IV-md-172
MeOD, 298 K




69.81
%T
37.25
3280.4
2362.3
1652.1
1553.9
1424.0
1377.1
1303.7
1268.6
1195.7
1138.7
1091.0
934.6
748.5
663.1
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
500
Me
N
O
HO
NH
Br
N
NH
O


02130504: Scan 13 (2.83 min) - Back
Base: 58.00 Int: 5.85e+006 Sample: VG 70-SE Positive CI-Methane
Sample: IV-MD-172
Instrument Resolution: 7,500
Theoretical Mass (C12H13BrN4O3): 341.0249214
Measured Mass: 341.0251115
Error: 0.55ppm
Me
HO
N
O
NH
Br
N
NH
O
105%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
58
100
75
88
150
165
215
245
263
325
341
371
40
100
150
200
250
300
350
400
m/z